ARCHIVES of INTERNAL MEDICINE

VOLUME 68 DECEMBER 1941 NUMBER 6

COPYRIGHT, 1941, BY THE AMERICAN MEDICAL ASSOCIATION

# ELLIPTIC ERYTHROCYTES IN MAN

HELEN WYANDT, M.S.
OMAHA

PAUL M. BANCROFT, M.D.
LINCOLN, NEB.
AND
THEODORE O. WINSHIP, M.D.
RIZAL, PHILIPPINE ISLANDS

In recent years attention has been directed to the fact that the red cells of an apparently healthy person are not necessarily round but may be distinctly elliptic or even sausage shaped. This condition has been recognized as a congenital anomaly, frequently called "ovalocytosis" in spite of the fact that the red cells are not strictly oval. This paper describes the incidence in 3 interrelated families of pure German extraction of 86 members with large numbers of such cells. This is the largest group for which this condition has been reported. In addition, we present features of the anomaly not previously recorded.

## REVIEW OF THE LITERATURE

Because reports of this condition have appeared in many languages and are not universally accessible, it seems desirable to present here a fairly complete review of the literature.

To Dresbach [1] goes the credit for reporting the first case of the anomaly. A mulatto medical student discovered during a class exercise that 90 per cent of his red cells were elliptic rather than round. They ranged in width from 3.9 to 4.8 microns and in length from 8.5 to 10.7 microns. Smears were shown to several pathologists, including Arneth, Ehrlich, Ewald and Ewing, who suggested that the anomaly might be of congenital or developmental origin. A brother of the student had only round cells; so the hereditary nature of the anomaly could not be proved. Because the student died shortly afterward, Flint [2] suggested

From the Department of Pathology and Bacteriology, University of Nebraska College of Medicine.

1. Dresbach, M.: Elliptical Human Red Corpuscles, Science **19**:469-470 (March 18) 1904.

2. Flint, A.: Elliptical Human Erythrocytes, Science **19**:796 (May 20) 1904.

that pernicious anemia or purpura might have caused the deformity of the cells, and death as well, which statement Dresbach [3] later refuted. This may not have been the first observation of the anomaly, since Ewald wrote Dresbach that a similar observation had been made at Königsburg, Germany, twenty or thirty years earlier. Lambrecht [4] reported that also in Königsburg, in 1860, Goltz had observed elliptocytosis in a woman. These 2 reports might have concerned the same person.

In 1914, Bishop [5] gave support to the concept of the congenital nature of the anomaly by reporting its occurrence in a man and his sister. Their father, another sister and her 2 children had normal cells. In both of the first-named persons the hemoglobin concentration was 100 per cent or above and the red cell count was 5,000,000 or more. The reticulocyte count and the result of fragility tests were normal.

The next case, that of a Negro, was reported by Sydenstricker,[6] in 1923. The patient had a mild degree of anemia, with 90 to 95 per cent of his red cells elliptic. In the same year, Huck and Bigelow [7] studied a case of the anomaly in much detail. The blood of a female medical student was observed daily for three weeks, but the number of deformed cells remained unchanged. Several times the student acted as a donor of blood for transfusions, and in 1 recipient no elliptic cells were found after two months, although there is no record of observations in the interim. The authors concluded that the shape was inherent in the cells themselves and was probably due to an anomaly of the blood-forming organs and not to outside influences.

The report by Lawrence,[8] in 1927, of a person whose blood contained 5 to 10 per cent sickle-shaped or elliptic red cells and whose brother, sister and niece had similar blood pictures, is open to question as presenting true examples of the anomaly, because of the scarcity of cells. He also reported 5 other instances in a series of 102 normal adults in which photomicrographs of the blood showed only rare elliptic cells and concluded that in these 5 cases the persons probably should not be

3. Dresbach, M.: Elliptical Human Erythrocytes, Science **21**:473 (March 24) 1905.

4. Lambrecht, K.: Die Elliptocytose (Ovalocytose) und ihre klinische Bedeutung, Ergebn. d. inn. Med. u. Kinderh. **55**:295-319, 1938.

5. Bishop, F. W.: Elliptical Human Erythrocytes, Arch. Int. Med. **14**:388-390 (Sept.) 1914.

6. Sydenstricker, V. P.: Elliptic Human Erythrocytes, J. A. M. A. **81**: 113-114 (July 14) 1923.

7. Huck, J. G., and Bigelow, R. M.: Poikilocytes in Otherwise Normal Blood (Elliptical Human Erythrocytes), Bull. Johns Hopkins Hosp. **34**:390-393 (Nov.) 1923.

8. Lawrence, J. S.: Elliptical and Sickle-Shaped Erythrocytes in Circulating Blood of White Persons, J. Clin. Investigation **5**:31-49 (Dec.) 1927.

considered as elliptic cell bearers. He expressed the belief that sickle cell anemia and elliptocytosis were related phenomena.

A new idea was introduced in 1928 by Günther,[9] who, by painstaking measurement of a large number of cells, separated human red cells into four classes on the basis of shape: class I, round; class II, roundish; class III, elliptic, and class IV, narrow elliptic. Of these, classes III and IV should not comprise more than 12 per cent, and class IV alone more than 0.4 per cent of the total number of red cells. He concluded that the elliptic form was the primary form of the vertebrate animal, inherent in the architectural structure of the cell. He reported 3 cases of tower skull, in 1 of which elliptic cells were present, and 2 additional isolated cases of the anomaly.

A report by van den Bergh,[10] in the same year, of a young girl whose father and 2 sisters also possessed elliptic red cells further pointed to the congenital nature of the anomaly. This concept was somewhat refuted by Bernhardt [11] after he observed a patient whose blood contained a large number of elliptic red cells, who had a moderate anemia, but whose father, mother, 2 sisters and their children had only round red cells. A few months later van den Bergh [12] reported another case of the anomaly, in which symptoms of hemolytic icterus were not accompanied by increased fragility. After splenectomy was performed, the icterus disappeared but the elliptic red cells remained.

In 1929, Hunter and Adams [13] definitely established the hereditary nature of the anomaly by their study of three generations of a Dutch-American family. The blood of 5 members of this family contained many elliptic red cells, while that of 7 more showed only a few such cells. A few years later, Hunter [14] added to this family tree 5 more American members whose blood contained a few elliptic red cells, and van den Bergh [15] added 4 more to the Dutch branch of this same family.

---

9. Günther, H.: Die klinische Bedeutung der Ellipsenformen der Erythrozyten, Deutsches Arch. f. klin. Med. **162**:215-230, 1928.

10. van den Bergh, A. A. H.: Elliptische rote Blutkörperchen, Arch. f. Verdauungskr. **43**:65-69 (March) 1928.

11. Bernhardt, H.: Ovalozytose der Erythrozyten als Anomalie, Deutsche med. Wchnschr. **7**:756-757 (April 15) 1928.

12. van den Bergh, A. A. H.: Elliptische rote Blutkörperchen, Addendum, Deutsche med. Wchnschr. **54**:1244 (July 27) 1928.

13. Hunter, W. C., and Adams, R. B.: Hematologic Study of Three Generations of White Family Showing Elliptical Erythrocytes, Ann. Int. Med. **2**: 1162-1174 (May) 1929.

14. Hunter, W. C.: Further Study of White Family Showing Elliptical Erythrocytes, Ann. Int. Med. **6**:775-781 (Dec.) 1932.

15. van den Bergh, A. A. H.: A propos des hématies elliptiques (l'ovalocytose), Rev. belge d. sc. méd. **3**:683-688 (June-July) 1931.

One more isolated case was reported in 1931 by Roth and Jung,[16] that of a 30 year old woman with icterus but with normal fragility of the red cells. Two sisters had round red cells. Two doubtful cases of the anomaly, with associated anemia and only a few elliptic red cells, and 1 apparently authentic case, with many elliptic red cells, were described by Lawrence,[17] who questioned whether, because of the abnormal type of cell, anemia might develop more readily in persons with elliptic red cells than in those with normal red cells.

One of the most comprehensive studies of the nature of the condition was made by Terry, Hollingsworth and Eugenio,[18] in 1932. They studied before death and at autopsy 2 unrelated patients who had died of disease. The elliptic cells were heavier, settled more rapidly and were less fragile than the round cells. They showed also that the cells were elliptic in the circulating blood and that their shape was not merely the result of artificial conditions after removal from the body.

Any doubt of the hereditary nature of the anomaly was dispelled by Cheney,[19] in the same year, by a study of 3 generations of a family in which 13 members had elliptocytosis and a fourteenth had only a few elliptic red cells. He established the transmission of elliptic red cells as a mendelian dominant and saw no sound basis for assuming any relation between the anomaly and anemia.

In 1933, Rotter[20] reported 9 cases of the anomaly in 3 generations of a white family in Costa Rica, although his record of the family tree was not complete. From Germany, in the same year, Grzegorzewski[21] reported 14 cases in 3 generations, with enough information to assume the carriers in another generation of ancestors. In 6 of these cases icterus and increased fragility of the red cells were also present, although Grzegorzewski stated that the anomaly had no relation to disease. Another large family was investigated, also in 1933, by Rosenow,[22] who found 12 members in 4 generations with numerous elliptic red cells.

---

16. Roth, O., and Jung, E.: Zur Kenntnis der Ovalozytose, Folia haemat. **44**:549-554 (July) 1931.

17. Lawrence, J. S.: Human Elliptical Erythrocytes, Am. J. M. Sc. **181**: 240-245 (Feb.) 1931.

18. Terry, M. C.; Hollingsworth, E. W., and Eugenio, V.: Elliptical Human Erythrocytes: Report of Two Cases, Arch. Path. **13**:193-206 (Feb.) 1932; M. Bull. Vet. Admin. **9**:7-17 (July) 1932.

19. Cheney, G.: Elliptic Human Erythrocytes, J. A. M. A. **98**:878-881 (March 12) 1932.

20. Rotter, W.: Elliptische rote Blutkörperchen als familiäre vererbbare Anomalie, Klin. Wchnschr. **12**:1777 (Nov. 11) 1933.

21. Grzegorzewski, H.: Ueber familiäres vorkommen elliptische Erythrozyten beim Menschen, Folia haemat. **50**:260-277, 1933.

22. Rosenow: Elliptische rote Blutkörperchen als familiäre vererbbare Anomalie, Klin. Wchnschr. **12**:481-482 (March 25) 1933.

Members of one branch of the family had a hereditary anomaly of the teeth, a defect of the superior lateral incisors, present in three generations. Rosenow found also that with venous stasis the percentage of elliptic red cells both in venous and in capillary blood increased. From Poland, Finkel [23] reported 2 instances of the anomaly in persons who also had anemia with sickle cells, accompanying massive infestation with lice. He expressed the belief that the two anomalies were identical, the different manifestations constituting only variations of the physicopathologic state which he called "dolichocythemia." He mentioned that the same blood picture, without an associated infestation with lice, occurred in children of these 2 persons although the number of children was not recorded.

An idea of the frequency with which the anomaly occurs was given in 1934 by McCarty,[24] who discovered 4 instances in the routine examination of 10,000 persons. Seven additional cases were found among the relatives of the 4 affected persons, all Negroes. McCarty found, too, that if the cells were washed with lecithin they all became round, while washing with cholesterol had no effect. In her series, the number of elliptic cells tended to decrease with succeeding generations, as a blended mendelian characteristic would do if the original trait was a sport. Pollock and Dameshek,[25] in the same year, confused the anomaly with the sickling trait by reporting the occurrence both of elliptic and of sickle-shaped cells in the blood of members of a Jewish family. The authors considered the two conditions different stages of the same phenomenon.

In 1935, Stephens and Tatelbaum [26] observed relative microcytosis and polycythemia accompanying elliptocytosis and an average red cell count of 6,470,000 in 8 members of one family. They considered it probable that in affected persons the potentiality for deformity was possessed by all mature erythrocytes, and perhaps to a lesser degree by the reticulocytes. That the change in shape occurred during or after the reticulocyte stage was shown by Schartum-Hansen.[27] He observed the anomaly in an anemic woman submitting to liver therapy, under which condition the reticulocyte response could be studied. A son of

23. Finkel, A.: Ovalocytemia and Drepanocytemia in People of the White Race, Polska gaz. lek. **12**:562 (July 23) 1933.

24. McCarty, S. H.: Elliptical Red Blood Cells in Man: Report of Eleven Cases, J. Lab. & Clin. Med. **19**:612-621 (March) 1934.

25. Pollock, L. H., and Dameshek, W.: Elongation of Red Blood Cells in Jewish Family, Am. J. M. Sc. **188**:822-834 (Dec.) 1934.

26. Stephens, D. J., and Tatelbaum, A. J.: Elliptical Human Erythrocytes: Observations of Size, Volume and Hemoglobin Content, J. Lab. & Clin. Med. **20**: 375-383 (Jan.) 1935.

27. Schartum-Hansen, H.: Die Genese der Ovalozyten, Acta med. Scandinav. **86**:348-360, 1935.

the woman also possessed the same type of red cell, but in fewer numbers. He expressed the belief that it was improbable that the mere 169 elliptic reticulocytes observed in the peripheral blood could represent the preliminary stage of 36,112 elliptic erythrocytes, while 790 round reticulocytes were the precursors of only 2,929 mature round erythrocytes. In his opinion, the elliptic cell was the end, or destructive, stage of all red corpuscles, the cause of the increased number of which in these 2 instances might be endocrine.

Babudieri [28] observed the anomaly in a mother and her 2 daughters with hypochromic anemia and in 2 members of another family. He thought that anemia might coexist with elliptocytosis but was not necessarily an accompaniment. In the blood of clinically healthy persons, the condition constituted a unique index of a particular constitutional state of the hemopoietic system, which in other persons might manifest itself in clinical anemia or even in pernicious anemia, depending on the intervention of various factors. In the same year Schemensky [29] reported 2 cases of the anomaly. He expressed the belief that the carriers of elliptic erythrocytes behaved normally and that the elliptic cell was not to be brought into causal relation to disease.

In 1937 reports of the condition became more numerous, and in general larger families were encountered. Janoušek, Štancl and Vacková [30] reported it in a Czech woman and her son and suggested that some of the abnormality of shape might be an artefact or the result of the Hamburg phenomenon. Horwitz [31] reported 1 case of the anomaly in the same year, and Ljudvinovsky,[32] from Russia, recorded 4 isolated cases, in which the available relatives all had only round red cells. Strauss and Daland [33] examined the blood of 36 members of a Russian-Jewish family, none of whom was known to have had jaundice or anemia. The mother, 3 of her 8 daughters and 6 of their 11 children showed elliptic red cells. Of these 10 persons, 27.7 to 61.0 per cent of the red cells showed a difference between the long and the short diameter of 2.5

28. Babudieri, B.: Alcuni nuovi casi di ellipsocitemia, Haematologica **17**: 73-76, 1936; Due casi di ellipsocitemia (ovalocitemia) Prima segnalazione in Italia, ibid. **17**:135-140, 1936.

29. Schemensky, W.: Die Ovalozytose, eine vererbbare Anomalie der Erythrocyten, Med. Welt **10**:1686-1687 (Nov. 21) 1936.

30. Janoušek, S.; Štancl, O., and Vacková, K.: Oval Erythrocytes in Man, Casop. lék. česk. **76**:872-876 (June 7) 1937.

31. Horwitz, S.: Thrombophlebitische Splenomegalie und Ovalozytose, Harefuah **12**:iii (May) 1937.

32. Ljudvinovsky, R. J.: On the Subject of Ovalocytosis, Terap. arch. **14**: 721-727, 1936.

33. Strauss, M. B., and Daland, G. A.: Hereditary Ovalocytosis (Human Elliptical Erythrocytes): Observations on Ten Cases in One Family, New England J. Med. **217**:100-103 (July 15) 1937.

microns or more, while in 5 persons with normal erythrocytes only 3.2 to 8.2 per cent of the cells showed that difference. The authors stated that the anomaly was transmitted as a mendelian dominant unit character. From Java, Kouwenaar [34] reported 14 cases in a Javanese family, the first to be reported from Asia. Bertelsen [35] observed 10 cases in a family near Copenhagen, Denmark, in 4 of which the liver and spleen were enlarged and in 2 of which there was icterus. He questioned whether the chronic infection which was present in these cases might cause the anemia or whether the elliptic cells with the accompanying anemia might be a predisposing factor in infection. In Downey's "Handbook of Hematology," Mason [36] has a section on ovalocytosis. He described 5 additional cases, in 1 of which there was accompanying anemia for which no cause was apparent. This association and the occurrence of similar cases in the literature led him to advance the theory that anemia might develop on, and was in some way related to, a vulnerable hemopoietic system, of which ovalocytosis was the direct expression. In this respect, the phenomenon might be analogous to that of sickle cell anemia and hemolytic icterus, in which the trait is more frequent than the disease.

In the same year, Lambrecht [4] reported 16 cases in 3 generations of 3 families living in Frankfurt-am-Main, Germany. He was the first to distinguish definitely between the normal person and the bearer of the anomaly by assuming that elliptocytosis existed if the sum of the cells characteristic of Günther's classes III and IV exceeded 25 per cent of the total number of red cells. He expressed the belief that this division was important for the recognition of what he called "latent carriers," persons having less than 25 per cent of elliptic red cells. In 2 of the families studied, anemia and jaundice with decreased resistance of the red cells were present, which led Lambrecht to assume a correlation between the anomaly of shape and the clinical signs. In his cases the presence of increased hemopoiesis led him to separate the condition into active, compensated and latent forms. Steinbrinck and Hahnelt [37] reported, also in 1938, 4 cases in 1 family and 2 cases in unrelated persons. They suggested the condition was a manifestation of a sort of atavism. Gigon,[38] also from Germany, observed 6 cases in three generations of a family. From America came two reports in addition to that

34. Kouwenaar, W.: Form of Erythrocytes with Special Consideration of Elliptocytosis, Geneesk. tijdschr. v. Nederl.-Indië **78**:827-840 (April 12) 1938.

35. Bertelsen, A.: Case of Familial Elliptocytosis, Ugesk. f. læger **100**:136-140 (Feb. 10) 1938.

36. Mason, V. R.: Ovalocytosis, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, pp. 2351-2360.

37. Steinbrinck, W., and Hahnelt: Ueber familiäre Ovalocytose, Deutsche med. Wchnschr. **54**:784-785 (May 27) 1938.

38. Gigon: Ovalozytose, München. med. Wchnschr. **85**:157 (Jan. 28) 1938.

of Mason. Florman and Wintrobe [39] recorded 11 cases in 3 families in which at least 40 per cent of the red cells were elliptic and 10 per cent were rod shaped. No member of any family, 2 of which were Negro and 1 of which was white, had anemia. They considered that the elliptic erythrocytes could be present in man as a familial condition and also in cases of a macrocytic type of anemia. Miller and Lucas [40] observed 9 cases in 4 generations of a family in Louisville, Ky. They suggested the existence of a secondary intraerythrocyte susceptibility to a primary extraerythrocyte influence, either or both of which might be congenital.

During 1939 all but 1 of the reports came from Europe. The largest family studied was reported by Lieberherr [41]; 22 instances of the anomaly were found among the 63 members whose blood was examined. In all cases microcytosis was present but not considered essential. Lieberherr expressed the belief that no definite relation existed between elliptic cells and the state of health and that any association with anemia was entirely accidental. Söderström [42] reported 3 isolated cases, in 2 of which the volume index was low, but no signs of hemolytic icterus were present. Vischer [43] found 12 persons with the anomaly in 3 generations of a Swiss family, with sufficient evidence to postulate the existence of 2 more in a fourth generation. He asserted that accurate measurement of the cells by Günther's method was unnecessary for recognition of the anomaly. In the cases which he reported, although the subjects were healthy, with no definite icterus or anemia, there was evidence of increased hemopoiesis in the bone marrow, borne out also by high reticulocyte counts. Transfusion experiments [44] showed also that the elliptic red cells had a life span of only twelve or thirteen days, shorter than that of normal erythrocytes. He concluded that there existed a predisposition to anemia, which was usually entirely compensated. Unless the compensation was broken by infection or increased activity of the spleen, the only hematologic evidence of the condition, other than the elliptic cells themselves, was increased erythropoiesis. One of the most comprehensive articles on elliptocytosis was that of Leitner [45] in which

39. Florman, A. L., and Wintrobe, M. W.: Human Elliptical Red Corpuscles, Bull. Johns Hopkins Hosp. **63**:200-220 (Oct.) 1938.

40. Miller, J. K., and Lucas, M. A.: Elliptical Erythrocytes in Human Blood, Am. J. Clin. Path. **8**:391-397 (July) 1938.

41. Lieberherr, W.: Ueber Ovalocytose, Helvet. med. acta **5**:589-596 (Nov.) 1938.

42. Söderström, N.: Ovalocytosis, Nord. med. tidskr. **16**:1996-2000 (Dec. 17) 1938.

43. Vischer, A.: Untersuchungen über Ovalozytose, Ztschr. f. klin. Med. **135**: 123-132, 1938.

44. Vischer, A.: Ueber die Lebensdauer der Erythrocyten. Beobachtungen bei Transfusionen mit Ovalozytenblut, Ztschr. f. klin. Med. **135**:133-136, 1938.

45. Leitner, S. J.: Die familiäre Elliptocytose als vererbbare Anomalie der Erythrocyten, Deutsches Arch. f. klin. Med. **183**:607-646, 1939.

he reported the cases of 4 full carriers and 2 part carriers. He also cited Schulten's [46] report of a family with 2 definite carriers of the anomaly and 2 whose blood contained only a few elliptic cells and expressed the belief that part carriers are important in the detection of family relationships. He asserted that anemia was not an essential accompaniment of elliptocytosis and that in most cases it was not demonstrable. According to his viewpoint, if families with normal red cells were as thoroughly investigated hematologically as those with elliptic red cells, just as many instances of unexplained anemia might be revealed. He observed slight microcytosis, with normal erythropoiesis, in the cases he reported and suggested that any increased hemolysis reported by other authors must be due to the fact that the elliptic cells were older and fragmented more readily than did the younger round cells. To him the anomaly was of important genetic significance, since it represented the smallest cell carrier of definite hereditary characteristics, whether arising as a result of mutation or as a direct peculiarity inherited through uncounted generations, whereby primary elliptic cells in the ancestors must be assumed. Giffin and Watkins [47] reported 8 cases of the anomaly at the Mayo Clinic, in 5 of which the elliptocytosis was regarded as accidental and not contributing to the patient's illness. In 3 cases in 1 family, it was associated with typical features of hemolytic icterus, although 1 member showed no clinical symptoms. In the 2 showing clinical symptoms of hemolytic icterus, elliptocytosis remained after splenectomy.

Reports which probably should not be included in a review of the literature of elliptic red cells are those by Fanconi [48] and Introzzi.[49] The former reported a case, observed through fourteen years, of primary hemolytic hyperchromic elliptocytanemia with icterus and anemia and a large number of elliptic cells, which responded poorly to splenectomy. He asserted that this condition was a disease entity which should be separated from familial hemolytic icterus and elliptocytosis. Introzzi discussed the case of a patient with hypochromic anemia, elliptocytosis, poikilocytosis, increased hemoglobin exchange and slight icterus. This patient, also, responded poorly to splenectomy. A similar blood pic-

46. Schulten, H.: Die Sternalpunktion als diagnostische Methode, Leipzig, Georg Thieme, 1936; cited by Leitner.[45]

47. Giffin, H. Z., and Watkins, C. H.: Ovalcytosis with Features of Hemolytic Icterus, Tr. A. Am. Physicians **54**:355-358, 1939.

48. Fanconi, G.: Die verschiedenen Formen der primären hämolytischen Anämien; die hyperchrome Elliptozytenanämie und ihre Differentialdiagnose gegenüber der Perniziosa und der Kugelzellanämie, Arch. f. Kinderh. **117**:1-32 1939.

49. Introzzi, P.: Anemia ipocromica splenomegalica emolitica con ovalocitosi (ellitticitosi), poichilocitosi ed aumento della resistenza osmotica der globuli rossi, Splenectomia, Haematologica **16**:525-579, 1935.

ture was found in a sister and a cousin of the patient. Introzzi expressed the belief that the elliptocytosis occurring in these persons was the same as that occurring in healthy ones.

The total number of cases of definite elliptocytosis reported in this summary is 246, occurring in 64 families. In 31 cases, representing 7 additional families, it is questionable, because of the small number of elliptic cells observed, whether the persons concerned were true carriers of the anomaly.

## EXPERIMENTAL PROCEDURE

In this study, the first case of the anomaly was discovered accidentally during an examination of the blood of D. B., who came to the dispensary of the University of Nebraska Hospital, Omaha, in October 1936, complaining of an axillary lymphadenopathy. At that time his hemoglobin concentration was 12.3 Gm. per hundred cubic centimeters, his red cell count was 4,900,000 and approximately 92 per cent of his red cells were either elliptic or rod shaped. His mother and 1 brother had similar blood pictures, while those of his father and sister showed only round red cells. Only round cells had been found in sections of tissue taken at autopsy of a male twin of the brother, who had died at the hospital several years before. The mother had 9 siblings and her father had 11, all of whom were living and were examined in this study. During the course of the investigation, 3 spouses were found who showed the same anomaly, and an attempt was made to test the various members of the families of 2 of them. In all, more than 600 persons were tested in these 3 families and in others distantly related by blood, in an attempt to discover a relationship between them or a common ancestor of the three. With the help of the Akademische Auslandsstelle and the Gesundheitsamt, blood was examined from 43 persons in Germany in the locality from which the ancestors of the 3 families emigrated in 1869. Records of family lineage were studied there also.

In the beginning, only dry smears and moist preparations of blood were made. No. 0 cover glasses were used, and the preparations were sealed with petrolatum. For those persons whose blood contained elliptic red cells, red cell counts, hemoglobin estimations, reticulocyte counts and blood group determinations were made with standard technics. Later, for a linkage study, the blood group was determined for all persons whose blood was examined for ellliptic red cells. A more detailed examination of 14 persons with elliptic cells included complete blood counts and determination of the icterus index, van den Bergh reaction, the red cell fragility, the hematocrit value and the cholesterol content of the blood. (Three and a half years later the blood of 1 of these persons was reexamined.) In addition, the red blood cells of several persons were measured with the euscope, according to the method of Sauder and Toomey,[50] and the individual red cells in a selected field of a moist preparation were measured daily for five days to determine the constancy of shape of the cells. Daily counts of the number of elliptic cells were made for 1 person for three weeks, as well as repeated estimations of the urobilinogen in the urine; the latter were made because of the increased red cell turnover reported by Lambrecht[4] and by Vischer.[43] Cord blood was obtained in 3 cases at the time of delivery. Counts of the elliptic cells

50. Sauder, H. R., and Toomey, J. A.: Rapid Measurement of Red Cells, Am. J. Dis. Child. **41**:823-828 (April) 1931.

in each instance were made on the moist preparations on the day on which the specimens were obtained and in an area in which the film was thin, rouleaux were absent and the cells were not distorted. Cells which showed a distinct difference between the long and the short diameter were considered elliptic. At least 600 cells were counted in each instance. These preparations were observed at intervals for several weeks. In addition, blood from 450 healthy medical students and nurses was examined, as well as blood smears from 1,000 patients consecutively admitted to the hospital, a fairly accurate cross section of the population of the state in general. This examination was considered necessary because of the large number of instances of the anomaly found during the course of the investigation. To ascertain whether the anomaly was inherent in the plasma or in the cells themselves, washed and unwashed suspensions of the cells were mixed with homologous normal serum and plasma, and washed and unwashed normal cells were added to the serum and plasma of elliptic cell carriers of the same blood group. An attempt was made also to substantiate the statement of Terry and associates [18] that the elliptic cells are heavier and less fragile than are normal red cells.

## RESULTS

*Definition of an Elliptic Cell Carrier.*—Among our first decisions was the number of elliptic cells required to warrant designating a person as an elliptic cell carrier. The incidence of elliptic red cells in the blood of the 450 students and nurses is indicated in the following tabulation:

| Percentage of Students and Nurses | Percentage of Elliptic Red Cells |
|---|---|
| 58 | 1 or less |
| 37 | 2 to 5 |
| 4 | 5 to 10 |
| 1 | 10 to 15 |

Of the 1,000 patients, 2 whose blood contained 29 and 38 per cent, respectively, of elliptic red cells had definite anemia and 1 whose blood had 22 per cent of such cells had no anemia. According to Günther,[9] in a normal person the sum of the red cells of classes III and IV should not exceed 12 per cent, or in rare instances 22 per cent. Florman and Wintrobe [39] restricted the anomaly to those persons with more than 40 per cent elliptic and 10 per cent rod-shaped cells, while Lambrecht [4] placed the dividing line at 25 per cent. Since no member of a family in this series in which there were no elliptic cell carriers had more than 15 per cent elliptic red cells unless anemia was present, 25 per cent was arbitrarily chosen as a conservative dividing line. Rarely were elliptic cell counts in the zone between 10 and 25 per cent encountered, while 40 per cent was the lowest number found in any definite case in our series and it was observed in a member of a fourth family who had married into one of the 3 families reported. We realize that estimations made in this manner are not as accurate as actual measurements by Günther's method or by Price-Jones curves, but we

found it possible with practice to check repeated estimations closely, so the procedure was continued. Lambrecht,[4] Leitner [45] and Schulten [46] have designated as part carriers persons with only a few elliptic red cells. We feel that the designation is not justified, because in our experience a true bearer of the anomaly will have more than 25 per cent of his cells definitely elliptic, while normal members of families in which elliptic cells occur have less than 10 per cent such cells, as do normal persons in general. The fact that the red cells may be caused to round up by irregularities of the slide or cover glass, as well as any pressure applied to the latter, may account for the cases in which only a few elliptic cells were reported.

*Genetic Observations.*—The genealogic charts of the three families studied are shown in figures 1, 2 and 3. Individual families which

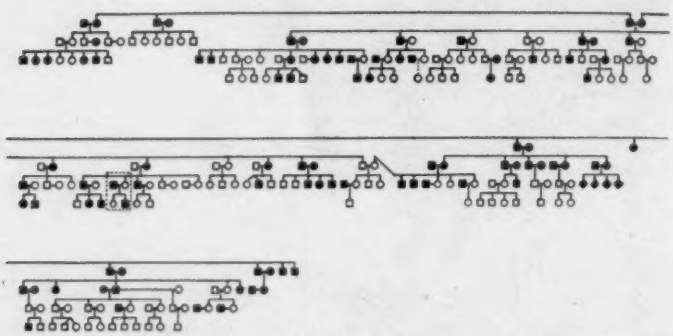


Fig. 1.—The incidence of elliptocytosis in family T. The following symbols bear the same significance for family T., family A (fig. 2) and family W (fig. 3): white square, a male with normal red cells; white circle, a female with normal red cells; black square, a male with elliptic red cells; black circle, a female with elliptic cells; square enclosing a cross, a male whose blood has not been examined for elliptic red cells; circle enclosing a cross, a female whose blood has not been examined for elliptic red cells, and diamond enclosing a cross, a person of unknown sex whose blood has not been examined for elliptic red cells. In figures 1, 2 and 3 a dotted line surrounding an individual family group indicates that the group appears also on one of the other two family charts.

belonged to two genealogic charts were counted with the family to which the elliptic cell parent belonged. On the chart of the family of the nonelliptic cell parent such an individual family is indicated by a dotted line. In the case of the family with 2 elliptic cell parents, the father and daughter are counted with his family. In all, 86 members of the three families showed elliptical cells. In the case of family T., the presence of the trait in 1 descendant of a brother of the mother (long dead) suggests that she, rather than the father, was the carrier

of the trait. In a personal communication Dr. Karl Nieberding, of Oldenburg, Germany, tells of the discovery of other members with elliptic cells in the same branch of family T. there, after one of us (H. W.) returned to America, but the war has prevented a detailed report of them. Twenty-eight instances of the anomaly occurred in family A., 28 in family W. and 30 in family T. (the original family).

In this series there were definitely more males with the anomaly than without it, as well as more affected males than females, especially

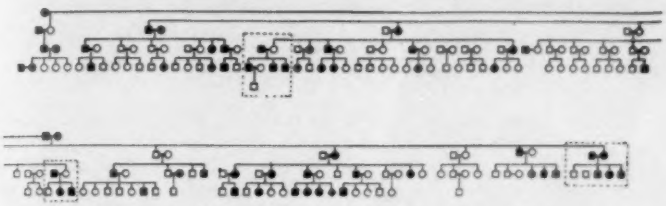


Fig. 2.—The incidence of elliptocytosis in family A.

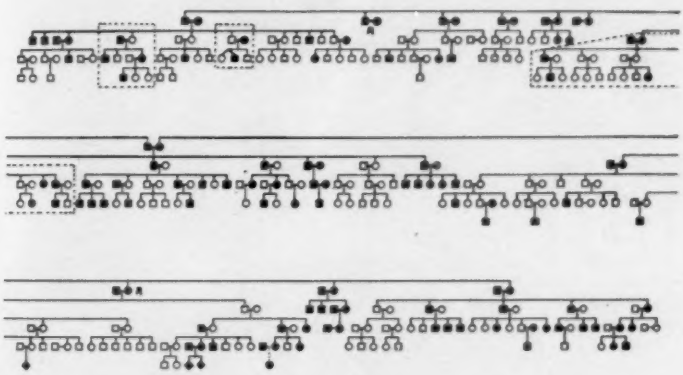


Fig. 3.—The incidence of elliptocytosis in family W.

when the father was the affected parent. When the total cases reported in the literature were considered, this apparent difference in sex incidence disappeared. This series of cases shows features not found in those previously reported. In 1 instance, both parents exhibited the anomaly. From this mating were born 2 sons with round cells, 2 sons who had died before this study was begun and 1 daughter with elliptic cells and, in addition, spherocytes and other evidences of hemolytic icterus, such as splenomegaly, markedly increased fragility of the red cells, high reticulocyte count and jaundice. Two pairs of twins are represented. Of a pair of fraternal twins, 1 had elliptic cells and the other had not.

It is difficult to say whether the other pair were identical, since 1 died at the age of 11 months. The living twin showed the anomaly, while sections of tissue made at autopsy of the other showed only round cells. That elliptic cells may be readily found in tissue sections from elliptic cell bearers was shown by Terry and associates.[18]

*Hematologic Studies.*—When sealed moist preparations of whole blood were allowed to stand in the laboratory, in the refrigerator or in the incubator (37.5 C.), the cells tended to round up, as shown in table 1, which gives measurements of the individual cells in a single high power field one, three and five days after the preparation was made. This rounding-up process was shown both by an increase in the shortest

TABLE 1.—*The Changes (in Microns) in the Diameters of Cells in Moist Preparations, Measured by Means of a Euscope*

| Cell No. | First Day | Third Day | Fifth Day |
|---|---|---|---|
| 1 | 5.08 × 11.45 | 5.83 × 9.58 | 6.04 × 8.12 |
| 2 | 5.00 × 11.45 | 5.83 × 10.20 | 6.25 × 9.14 |
| 3 | 6.04 × 9.37 | 6.66 × 6.87 | 6.66 × 6.87 |
| 4 | 5.31 × 10.20 | 5.62 × 9.14 | 5.83 × 8.95 |
| 5 | 3.33 × 8.54 | 5.31 × 8.12 | 5.83 × 8.12 |
| 6 | 5.41 × 10.00 | 5.62 × 9.14 | 6.25 × 8.12 |
| 7 | 6.45 × 11.04 | 6.45 × 10.64 | 6.45 × 9.14 |
| 8 | 5.83 × 10.41 | 6.04 × 9.79 | 6.25 × 8.95 |
| 9 | 4.79 × 12.29 | 5.00 × 10.00 | 5.00 × 9.58 |
| 10 | 5.41 × 9.79 | 5.62 × 9.58 | 5.62 × 9.37 |
| 11 | 3.33 × 8.70 | 5.00 × 7.70 | 5.41 × 7.29 |
| 12 | 6.25 × 10.00 | 6.87 × 7.91 | 6.87 × 7.08 |
| 13 | 5.00 × 10.41 | 5.41 × 8.12 | 5.62 × 7.29 |
| 14 | 4.37 × 9.58 | 4.79 × 8.71 | 5.41 × 7.29 |
| 15 | 4.16 × 10.41 | 4.16 × 9.58 | 4.16 × 9.37 |
| 16 | 5.31 × 11.25 | 5.31 × 10.64 | 5.31 × 8.95 |

diameter and by a decrease in the longest diameter of the individual cells. Preparations kept for three to four weeks showed few elliptic cells. At the end of four weeks, unidentified large brown crystals resembling a sheaf of wheat appeared regularly in mounts of elliptic cells as the cells began to disappear and rarely in the preparations of round cells. The significance of this phenomenon was not determined.

To establish the constancy of shape of the cells of any given person, counts were made daily on 1 subject during the course of a three and a half week stay in the hospital. The percentage of elliptic cells varied from 88 to 92, while that of the sausage-shaped cells ranged between 17 and 25. This constancy agrees with that reported by Huck and Bigelow [7] and by Leitner,[45] while Pollock and Dameshek [25] found diurnal variation. On one day, one of four preparations had twice as many sausage forms as the other three mounts made at the same time. Since the technic of washing the slides and cover slips and making the preparations was identical, as nearly as one could tell, we were at a

loss to explain this difference. It does suggest, however, that there may be some as yet unidentified outside or inside influence capable of altering the shape of the red cell which might be a factor in this anomaly.

Preparations of these persons' cells, washed or unwashed, mixed with normal serum or plasma, however, showed no alteration in the shape of the cells for several days, although after three weeks all but a few cells had become round, even though well preserved. Since this happened even in moist preparations of whole blood of the elliptic cell carriers, no significance was attached to the fact that the cells became round in the foreign plasma also. Practically all observers have noted that there is no alteration in shape either of elliptic cells suspended in normal plasma or of normal red cells in plasma of an elliptic cell carrier. This has been interpreted by most authors to mean that the elliptic shape is inherent in the structure of the cell itself.

Sternal punctures were made in 2 cases. In each, approximately 80 per cent of the non-nucleated red cells were elliptic, although all of the nucleated erythrocytes were round or nearly so. There was no evidence of increased erythropoiesis.

Reticulocyte counts were slightly elevated, the percentage of these cells ranging from 1.6 to 13. In general, the greater number of the cells showing basophilia were round, in the proportion of 2 to 10 round reticulocytes to 1 elliptic cell, with 2 exceptions. F. M. (family T.) had 2.2 per cent round reticulocytes and 3.6 per cent elliptic cells, while E. A. (family T.) had 4 and 9.6 per cent, respectively. The fact that the majority of the reticulocytes, as well as the normoblasts in the bone marrow, are round suggests that the elliptic shape is assumed during or after the reticulocyte stage, as has been well demonstrated by Schartum-Hansen.[27] To reconcile the fact that the cells assume the elliptic shape after leaving the bone marrow and coming in contact with the plasma, while normal cells are uninfluenced by the same plasma, Miller and Lucas[40] have suggested a secondary intraerythrocyte susceptibility to a primary extraerythrocyte influence, either or both of which might be inherited. On the other hand, both round and elliptic cells are found in the plasma of the same person, which speaks against any action of the plasma alone.

We were unable to substantiate the assertion by Terry and his associates[18] that the elliptic red cells settled more readily, were heavier and were less fragile than normal red cells, possibly because in the blood of persons in this series of cases the round cells were too few to allow accurate separation from the elliptic ones.

It is in respect to a possible relationship of the anomaly to anemia that considerable controversy exists. In our cases the subjects were singularly free from any type of anemia, and the individual family members were unusually healthy and long lived. In only 1 instance was definite anemia present. A child, E. A. (table 2), both of whose

TABLE 2.—*Results of Laboratory Tests*

| Patient | Age, Yr. | Degree of Elliptocytosis, Percentage | Red Cell Count | Hemoglobin, Gm. per 100 Cc. | Reticulocytes, Percentage | | Mean Corpuscular Volume, Cubic Microns | Mean Corpuscular Hemoglobin | Mean Corpuscular Hemoglobin Concentration | Icterus Index | Van den Bergh Reaction | | Red Cell Fragility | | Cholesterol, Mg. per 100 Cc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Round | Elliptic | | | | | Direct | Indirect, Mg. per 100 Cc. | Beginning Hemolysis | Complete | |
| F. A. | 71 | 83 | 5,400,000 | 16.2 | 2.0 | 1.0 | 85.5 | 31.5 | 37.1 | 6 | Negative | 0.3 | 0.40% | 0.30% NaCl | 218 |
| L. A. | 69 | 83 | 5,200,000 | 16.5 | ... | ... | 90.0 | 33.6 | 37.0 | 6 | Negative | 0.3 | 0.44% | 0.30% NaCl | 280 |
| O. A. | 52 | 87 | 5,700,000 | 17.8 | 2.7 | 0.6 | 92.0 | 33.5 | 36.4 | 7 | Negative | 0.2 | 0.48% | 0.34% NaCl | 224 |
| E. A. | 49 | 95 | 4,500,000 | 13.1 | 2.3 | 1.3 | 89.0 | 31.4 | 35.2 | 6 | Negative | 0.1 | 0.50% | 0.34% NaCl | 201 |
| W. A. | 43 | 82 | 5,400,000 | 15.5 | ... | ... | 87.0 | 32.0 | 35.2 | .. | ..... | ... | 0.40% | 0.28% NaCl | 215 |
| H. C. | 32 | 73 | 5,100,000 | 14.4 | 2.2 | 0.7 | 86.0 | 36.0 | 35.3 | 3 | Negative | 0.1 | 0.44% | 0.32% NaCl | 218 |
| P. A. | 40 | 91 | 4,800,000 | 15.7 | 1.4 | 0.4 | 98.0 | 34.5 | 35.2 | 6 | Negative | 0.2 | 0.48% | 0.32% NaCl | 176 |
| H. A. | 28 | 80 | 5,400,000 | 16.5 | 1.3 | 0.2 | 95.0 | 32.0 | 34.0 | 6 | Negative | 0.2 | 0.48% | 0.34% NaCl | 165 |
| M. A. | 27 | 96 | 5,000,000 | 15.2 | ... | ... | 88.0 | 32.5 | 37.0 | 8 | Negative | 0.4 | 0.46% | 0.32% NaCl | 228 |
| M. B.* | 36 | 92 | 4,800,000 | 13.6 | 2.6 | 1.2 | 85.0 | 33.0 | 38.8 | 5 | Negative | 0.2 | 0.46% | 0.30% NaCl | 184 |
| C. B. | 28 | 96 | 5,000,000 | 13.4 | ... | ... | 79.4 | 26.4 | 33.2 | 10 | Negative | 0.5 | 0.50% | 0.34% NaCl | ... |
| N. M. | 16 | 93 | 4,900,000 | 14.9 | 2.0 | 0.2 | 85.5 | 32.8 | 38.3 | 9 | Negative | 0.4 | 0.44% | 0.32% NaCl | 160 |
| E. A. | 12 | 81 | 4,200,000 | 10.9 | 4.0 | 9.0 | 75.5 | 28.0 | 36.0 | 20 | Negative | 1.6 | 0.80% | 0.20% NaCl | 140 |
| D. B. | 9 | 92 | 4,900,000 | 12.3 | 3.0 | 0.6 | 74.0 | 27.5 | 35.0 | .. | Negative | 0.1 | 0.48% | 0.30% NaCl | 167 |
| M. B.* | 40 | 90 | 4,100,000 | 11.6 | ... | ... | 90.1 | 28.2 | 31.3 | 7 | Negative | 0.2 | 0.40% | 0.30% NaCl | 207 |

* The same patient. The second tests were made three and a half years after the first ones.

parents had elliptic cells in large numbers, had a red cell count of 4,200,000 and a hemoglobin concentration of 9.8 Gm. per hundred cubic centimeters. In addition, she had a positive indirect van den Bergh reaction, markedly increased red cell fragility, a high reticulocyte count and spherocytosis, as well as an enlarged spleen, an icteric tint to the skin and a history of previous hemolytic crises typical of those associated with familial hemolytic icterus. In figure 4, a photomicrograph of her blood can be compared with one of blood taken from an elliptic cell carrier. The fragility of the red cells of the mother and father was normal, as were the icterus index, the van den Bergh reaction and the reticulocyte count; no definite spherocytes were seen. Neither had any knowledge of having had jaundice or of its occurrence in any member of the immediate families, besides the daughter. Two living children have always been healthy, but they refused to have samples of blood taken for determining the icterus index and for making fragility tests. One other child died suddenly in infancy, and another died of peritonitis after an appendectomy. Splenomegaly and jaundice have been reported in elliptic cell bearers by Bernhardt,[11] Introzzi,[49] van den Bergh,[12] Grzegorzewski,[21] and Bertelsen[35]; jaundice alone, by Roth and Jung,[16] Lambrecht[4] and Fanconi,[48] and increased red cell fragility, by Ljudvinovsky,[32] Pollock and Dameshek,[25] Vischer[43] and Babudieri,[28] in addition to van den Bergh, Roth and Jung and Grzegorzewski. Except for the increased fragility, the blood picture for this child is similar to that reported by Introzzi[49] as one of hypochromic anemia, with elliptocytosis and poikilocytosis, which he considered a distinct disease entity, separate both from elliptocytosis and from familial hemolytic icterus. The definite occurrence in E. A.'s blood both of elliptic cells and of spherocytes suggests the simultaneous occurrence of the two red cell anomalies, in spite of the absence of spherocytes in the blood of either parent. The fact that both father and mother are elliptic cell bearers, the only case of this on record, may have some bearing.

Additional evidence that spherocytosis and elliptocytosis can coexist is found in the cases reported by Introzzi[49] and Fanconi[48]; while possibly the condition was not true elliptocytosis in either case, both spherocytes and elliptical cells did exist simultaneously. Dr. John C. Sharpe,[51] of Omaha, had 1 case in which both types of cells occurred, together with typical clinical and laboratory signs of familial hemolytic icterus. After splenectomy, both types of cell persisted, although clinical symptoms of hemolytic icterus disappeared. Van den Bergh reported an instance in which signs of hemolytic icterus, with the exception of increased red cell fragility, were present. These signs disappeared after splenectomy, while the elliptic cells persisted. Two patients of Giffin and Watkins[47] showed both clinical symptoms of true familial hemo-

51. Sharpe, J. C.: Personal communication to the authors.

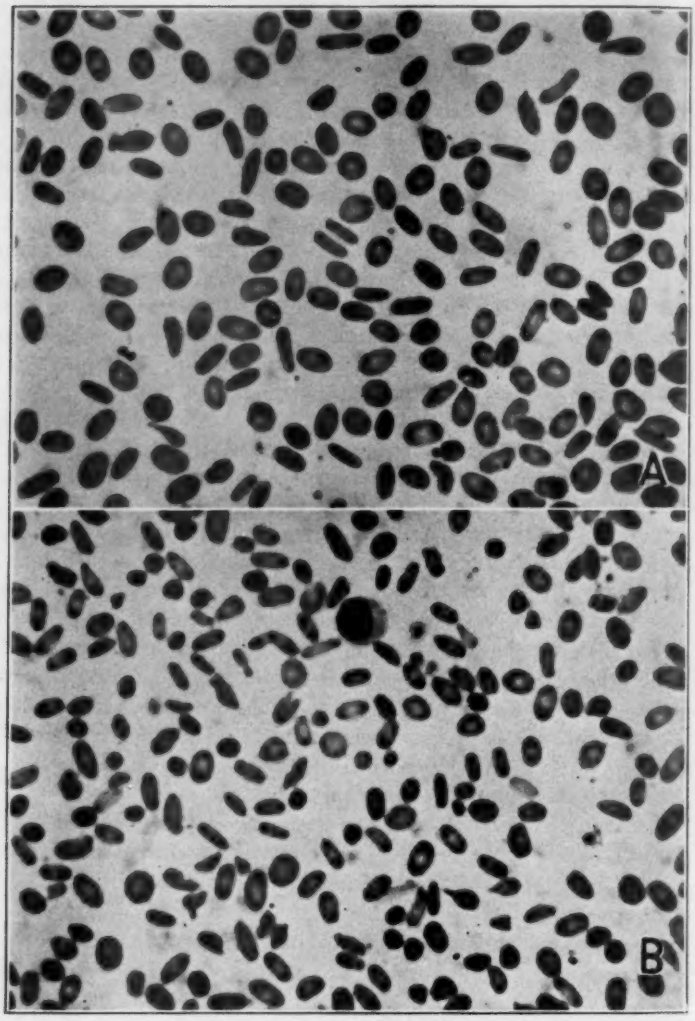



Fig. 4.—*A*, elliptic red cells in the blood of a healthy carrier. *B*, elliptic red cells and spherocytes in the blood of patient E. A.

lytic icterus and elliptic cells in large numbers; the elliptic cells persisted after splenectomy. Because the term hemolytic anemia covers such a variety of conditions resulting from such different causes, with only increased hemolysis in common, it does not seem unreasonable that atypical cases of a hemolytic type of anemia might occur in an elliptic cell family, as well as in a family with only round red cells. These cases suggest, however, that true hemolytic icterus of familial type with spherocytes, increased fragility of the red cells and other laboratory and clinical signs can occur in elliptic cell bearers. If a definite relation could be established between true hemolytic icterus with spherocytosis and elliptocytosis with spherocytosis, it would be a distinct hematologic advance.

With 3 exceptions, 2 of them in children, the mean corpuscular volume, the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration of the persons examined were within normal limits. In the 3 exceptions, there was slight microcytosis. This has been reported by Lieberherr,[41] Stephens and Tatelbaum [26] and Leitner,[45] but the majority of investigators found a normal cell volume in spite of the great variation in shape of the red cells.

In the rest of the series the occurrence of red cell counts and hemoglobin estimations which were normal or above led us to think that slight polycythemia might accompany this elliptocytosis, as was found by Stephens and Tatelbaum.[26] Round cell members of the same families, however, showed similar polycythemia. In spite of the 1 subject with anemia (E. A.), we feel that this large series of unusually healthy and long-lived carriers should speak strongly against any obligatory relationship between the anomaly and anemia. This conclusion is in agreement with those of Gigon,[38] Rosenow,[22] Florman and Wintrobe,[39] Vischer,[43] Leitner,[45] Schemensky,[29] Lieberherr,[41] Miller and Lucas [40] and Strauss and Daland.[33]

On the other hand, Mason [36] points to the cases of elliptocytosis in the literature in which associated anemia is unexplained (Hunter and Adams,[13] van den Bergh [12] and Lawrence [52]) and reports another as evidence that anemia developed on, and was in some way related to, a vulnerable hemopoietic system of which elliptocytosis was a direct expression. Vischer [43] expressed the belief that the more rapid hemoglobin turnover was evidence of a predisposition to anemia, and Lambrecht [4] asserted that anemia was evidence of decompensation accompanying the increased hemolysis which he observed in the cases he reported. The blood of 1 member of our series, M. B. (family T.), which was examined many times during three weeks, showed no evidence of increased hemolysis detectable by repeated determinations of

52. Lawrence (footnotes 8 and 17).

the urobilinogen in the urine, the icterus index or the van den Bergh reaction. During this period, she underwent a serious gynecologic operation which might have precipitated a break in the compensation had increased hemolysis been a factor. In addition, bone marrow studies made on this subject during this time showed normal erythropoiesis. There may be considerable truth in the statement by Leitner [45] that if families with normal red cells were investigated hematologically as thoroughly as families in which elliptocytosis occurs, just as many cases of unexplained anemia might be detected as have been reported in connection with that anomaly.

In analogy to the red cell anomalies of spherocytosis and drepanocytosis, in which the trait is much more common than the accompanying disease, it seems logical that a disease entity might accompany this red cell anomaly also. This supposition is made even more logical by the fact that in certain forms of anemia, especially pernicious anemia [9] and other types of macrocytic anemia,[39] as well as that accompanying lymphatic leukemia, a relatively large number of the red cells are elliptic, while spherocytes and sickle cells occur only as an anomaly. In addition, a few such cells are found in the blood of almost all normal persons. The presence of this type of cell both in a normal person and in association with a definite pathologic condition of the hemopoietic system suggests that some variation of the same force or factor is responsible in both cases. However, the various types of anemia which have been reported in elliptic cell bearers have been too diverse to constitute a basis for any distinct clinical entity comparable to familial hemolytic icterus or sickle cell anemia, and the incidence has been too inconstant to indicate an essential relationship. It seems that our series of cases should add further evidence that the anomaly has no definite relation to disease.

The cause of the anomaly is entirely unknown. It has been shown conclusively that the change to the elliptic shape takes place during or after the reticulocyte stage and is inherent in the structure of the cell itself. For that reason, it has been suggested by Schartum-Hansen [27] and Leitner [45] that the elliptic cell is an old form of erythrocyte—an end stage, as it were—since a few such cells are present in the blood of all normal persons. Leitner expressed the belief that the shorter life span of the elliptic cells, as indicated by the transfusion experiments of Vischer,[44] was due to the fact that the elliptic cells were older, and consequently were closer to the end of their life span.

With the exception of the mammals, the erythrocytes of vertebrate animals are elliptic and nucleated. Of the mammals, the Camelidae alone have elliptic, non-nucleated cells. The change from nucleated elliptic cells to non-nucleated cells is demonstrated in two families of salamanders, represented by Batrachoseps attenuates and Aneides

lugubris [53] which are identical, except the structure of the gills and red blood cells. In the former, which has but rudimentary gills, the nuclei from the red cells have been lost, possibly to increase the oxygen-carrying capacity of the cell to compensate for the lack of oxygenating surface in the gills. The change from elliptic to round cell may have resulted in a manner equally logical. In fact, Terry and his associates [18] suggested that elliptocytosis might furnish a link between the marine vertebrates and man. According to them, the elliptic shape might have been assumed from some earlier necessity, theoretically, a less constant plasma, while the disk might have developed later as an adaptation to conditions, such as a fully developed species-specific plasma, in which such degree of rigidity of form was no longer necessary or advantageous. Such an adaptation of cells and plasma in progress and not yet complete can be seen in the blood groups in which the agglutinins are not present in the full amount at birth.[54] That a certain adaptation of a similar type occurs in this condition is exemplified by the case reported by Hunter,[14] and by 1 case of this series, in which the elliptic cells in the blood from the umbilical cord were few but increased markedly in the circulating blood after birth. In the former case, they increased to 41.4 per cent oval and 1.6 per cent elongated cells three months after birth. In the latter, 11 per cent of the cells were elliptic at birth, but had increased to 80 per cent four months later.

This observation adds certain weight to the view of Schartum-Hansen [27] and of Leitner [45] that the elliptic cell is an older form, since the blood of a newborn infant also shows a higher number of young red cells than does that of an adult, with 1 to 24 normoblasts per 100 leukocytes and a percentage of reticulocytes as high as 20.[55] Within a week or two after birth, these values reach adult levels. In the case reported by Hunter, the elliptic cells increased markedly during the first week of life. This change also might indicate some process of adaptation of cells to plasma, in progress but not complete, as suggested before.

Various causes other than age have been suggested, such as faulty erythropoiesis, defective bone marrow, a mutation and some form of atavism, but no definite one has been established.

Recent reports indicate that the anomaly is more common than hitherto considered. The incidence has been given as 0.04 to 3 per cent, with the lower figure probably the more correct.[40] During the four

53. Emmel, V. E.: Hematological and Respiratory Conditions in the Larval Stages of the Lungless Amphibians Batrachoseps Attenuates and Aneides Lugubris, Anat. Rec. **21**:56, 1921.

54. Wiener, A. S.: Blood Groups and Blood Transfusion, Springfield, Ill., Charles C. Thomas, Publisher, 1935, pp. 15-19.

55. Wollstein, M., in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, pp. 930-932.

years in which this study has been in progress only 2 additional cases have been found in the course of approximately 7,000 examinations, although in a large number of smears as many as 10 per cent of the red cells were elliptic. Florman and Wintrobe [39] reported that in 89 per cent of persons without anemia and in 98 per cent of persons with anemia, elliptic cells were found. One to 15 per cent of the cells of the former were elliptic, while in 12 per cent of those with anemia more than 25 per cent of the cells were elliptic. The anomaly has been reported for almost every race except Chinese, Japanese and Hindu, with the largest number of cases reported from among the German people.

According to Strauss and Daland,[38] elliptocytosis is transmitted as a simple mendelian dominant unit character, to which statement practically all observers have agreed. The individual family in this series in which both parents and 1 child show the anomaly and 2 children do not definitely proves that the anomaly could not be a recessive characteristic, if there was any need for such proof. In only 1 instance, reported by Bernhardt,[11] has the anomaly been observed in the offspring of parents both of whom had only round red cells, an occurrence which might be possible if it arose as a mutation.

The medicolegal significance has been suggested by Miller and Lucas [40] and should be emphasized. Although rare, the occurrence of elliptocytosis might aid in the identification both of person and of paternity. This possibility was realized in the case of another family studied by two of the authors (H. W. and P. B.) but not reported in this series. In addition, the ease of recognition of the anomaly makes it valuable in linkage studies of various inherited characteristics.

Several questions remain to be settled. The relation of the anomaly to anemia has not been definitely proved, although this large series of cases should add support to the theory that the two conditions are not definitely correlated. There is a question whether there might not be two entities, simple elliptocytosis and a condition in which elliptic cells, as well as poikilocytes and even spherocytes, coexist with a definite degree of anemia. Whether any abnormal characteristics accompany the condition has not been settled entirely. Tower skull [9] and anomalies of the teeth and the jaws [50] have been reported. In this series no such anomalies were found. Its relation to blood groups has not been settled. The etiology is unknown. Another question to be settled is the significance of so-called part carriers, mentioned by Lambrecht, Leitner and Schulten, as well as the importance of the few elliptic cells constantly present in the blood of members of nonelliptic cell families and the larger number of such cells found in persons with anemia.

56. Finkel.[23] Lambrecht.[4]

## SUMMARY

Eighty-six new cases of elliptocytosis in 3 large families of German extraction are reported. In this series, the trait was more frequent in males than in females.

The occurrence of this condition in 2 pairs of twins, is reported; 1 member of each pair had elliptic red cells, while the other had round ones.

One family is reported in which both the father and the mother had elliptic cells in large numbers.

Laboratory data are given for 14 cases, as well as experimental data to show some of the characteristics of elliptic cells.

In 1 case there was laboratory and clinical evidence of both elliptocytosis and spherocytosis.

The fact that all other members were free from anemia, unusually healthy and long lived, lends support to the opinion that the anomaly has no definite relation to disease.

# EFFICACY OF INTRAVENOUS SODIUM BICARBONATE THERAPY IN THE TREATMENT OF DIABETIC KETOSIS

LOUIS B. OWENS, M.D.
Instructor in Internal Medicine, University of Cincinnati College of Medicine, and Director of the Diabetic Clinic, Cincinnati General Hospital

JACKSON WRIGHT, M.D.*
Clinician, Diabetic Clinic, Cincinnati General Hospital
AND
EDNA BROWN, M.S.‡
CINCINNATI

Intravenous administration of sodium bicarbonate was first used in the treatment of diabetic ketosis in 1886 [1]; although it has been a recognized procedure in most clinics for the ensuing fifty-five years, there is even yet little agreement as to its efficacy. Of the various reasons for this discrepancy, one is most apparent. So many different prognostic and therapeutic factors influence the outcome of the disease that evaluation of any single procedure, such as administration of sodium bicarbonate, is rendered difficult. The purpose of this paper is twofold, to discuss the effect of intravenous administration of sodium bicarbonate on blood sugar, carbon dioxide–combining power and ketones in the blood and urine during the treatment of diabetic ketosis and to report the effect of sodium bicarbonate therapy on coma mortality in 154 cases of ketosis, which were classified in five groups according to severity of the condition.

Not all of the chemical changes associated with diabetic ketosis can be explained in detail, but the reasons for the increased number of ketones in the blood and the lowered level of bicarbonate in the plasma are fairly well understood. Carbohydrate metabolism is interfered with during the development of diabetic ketosis, so abnormally large quantities of fat are broken down. Ketones, the intermediary products of fat combustion, occur in excess. Some are exhaled through the lungs or are oxidized directly in the tissues, but the greater number appear in

---

* Research Fellow in Diabetes, University of Cincinnati.

‡ Research Assistant in Medicine, University of Cincinnati.

From the Department of Internal Medicine, University of Cincinnati, and the Diabetic Clinic, Cincinnati General Hospital.

1. Wolpe, S.: Untersuchungen über die Oxybuttersäure des diabetischen Harns, Thesis, Königsberg, Leipzig, J. B. Hirschfeld, 1886.

the urine. Many ketones are organic acids as well, and before excretion can take place the sodium salts of the various acids are formed. The sodium ions for this reaction are drawn from the alkali reserve or the total base content of the blood. Since the effect of the sodium ions as potential alkali is lost once the salts are excreted in the urine and since ordinarily no steps are taken to replenish the reserves of sodium during the development of ketosis, the alkali reserve is soon exhausted and acidosis results.

The carbon dioxide–combining power is a measure only of the changes in the electrolytes in the blood, or the degree of acidosis. On the other hand, determination of the ketones in the blood measures directly the disturbance of fat metabolism and indirectly the disturbance of carbohydrate metabolism. Since ketones are formed only from fats and since fats are burned abnormally, because in the presence of uncontrolled diabetes the body is unable to utilize carbohydrates properly, measurement of the blood ketones affords a reliable index of the severity of the underlying metabolic changes.

The problem of death from diabetic ketosis is not solved by correcting the blood sugar, blood ketones and carbon dioxide–combining power. Many patients with ketosis have died, though they were chemically cured. The mental state of the patient and the duration of mental symptoms have been found to be more closely related to the eventual outcome than have other factors.[2] The amount of treatment, the age of the patient, the presence of circulatory collapse and infection all play a part in recovery. It was thought wise, therefore, to take these factors into consideration and then compare the mortality for patients treated with sodium bicarbonate with that for patients, not so treated, to determine whether practical benefit results from its administration.

## METHOD

In 12 unselected cases of severe diabetic ketosis the usual forms of therapy (parenteral administration of physiologic solution of sodium chloride, insulin and dextrose) were started. Fifteen hundred cubic centimeters of physiologic solution of sodium chloride was given on admission to the hospital and repeated as necessary. Insulin was given hypodermically at the rate of 40 to 50 units an hour, until the sugar in the blood and urine approached normal limits. From then on the hourly dose of insulin was reduced according to the individual needs of the patient. Dextrose was administered when the level of sugar in the blood approached normal if acetone still persisted in the urine.

Samples of blood were drawn and oxalated on admission and every three hours thereafter until the ninth hour. Determinations of dextrose, carbon dioxide–combining power and ketones were made on each sample. In 4 cases the total output of urine was collected for three hour periods and preserved for determination of ketones. The dextrose in the blood was measured by the method of Somogyi,

2. Owens, L. B., and Rockwern, S.: Prognosis of Diabetic Coma: Basic Importance of Mental State, Am. J. M. Sc. **198**:252-260, 1939.

Shaffer and Hartman.[3] The carbon dioxide-combining power of the serum was determined according to the method of Peters and Van Slyke,[4] and the ketones in the blood and urine, by the Van Slyke method, with Denige's reagent.[5]

In 9 of the 12 cases of diabetic ketosis intravenous administration of a 5 per cent solution of sodium bicarbonate was started either immediately or three hours after admission. The remaining 3 cases, in which no sodium bicarbonate was given, were used as controls. Pertinent data for these 12 cases are set forth in figures 1 and 2.

The mortality rate was also studied in 154 consecutive cases of diabetic patients who were admitted to the Cincinnati General Hospital for ketosis. Since the terms "ketosis" and "acidosis" are used rather loosely in many clinics, certain criteria were set up as a basis of selection of cases for this study. The minimum requirements were evidence of uncontrolled diabetes severe enough to require hospital treatment, presence of sugar and acetone in the urine, initial blood sugar over 200 mg. per hundred cubic centimeters and carbon dioxide-combining power under 30 volumes per cent. In most cases either drowsiness or unconsciousness was

*Relation Between Therapy with Intravenous Administration of Sodium Bicarbonate and Mortality in One Hundred and Fifty-Four Cases of Diabetic Ketosis*

| Intensity of Ketosis | 47 Cases in Which 10 Gm. (or More) of Sodium Bicarbonate Was Administered | | | | 107 Control Cases in Which No Sodium Bicarbonate Was Administered | | | |
|---|---|---|---|---|---|---|---|---|
| | Recovery | | Death | | Recovery | | Death | |
| | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| Extremely mild..... | 1 | 100 | 0 | 0 | 8 | 100 | 0 | 0 |
| Mild..... | 4 | 100 | 0 | 0 | 17 | 95 | 1 | 5 |
| Moderately severe..... | 9 | 60 | 6 | 40 | 21 | 67 | 11 | 33 |
| Severe..... | 7 | 54 | 6 | 46 | 17 | 53 | 15 | 47 |
| Extremely severe..... | 1 | 8 | 13 | 92 | 1 | 6 | 16 | 94 |

also present, and in many cases nausea, vomiting, abdominal pain and Kussmaul respirations were observed as well.

The 154 cases in which these criteria were fulfilled were divided into five groups, according to the classification described by Rabinowitch and associates,[6] which takes into consideration such factors as age, duration of mental symptoms, degree of consciousness, the presence of coffee ground vomitus, the presence of infection, blood pressure, plasma carbon dioxide-combining power, the level of urea in the blood and the presence of such associated conditions as tuberculosis, heart disease, vascular sclerosis and pregnancy. The results of this analysis are given in the table.

3. Somogyi, M.: A Method for the Preparation of Blood Filtrates for the Determination of Blood Sugar, J. Biol. Chem. **86**:655-663, 1930. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, St. Louis, C. V. Mosby Company, 1938, pp. 173-174.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, pp. 296-298.

5. Peters and Van Slyke,[4] pp. 639-641.

6. Rabinowitch, I. M.; Fowler, A. F., and Bensley, E. H.: Diabetic Coma: Investigation of Mortalities and Report on Severity Index for Comparative Studies, Ann. Int. Med. **12**:1403-1428, 1939.

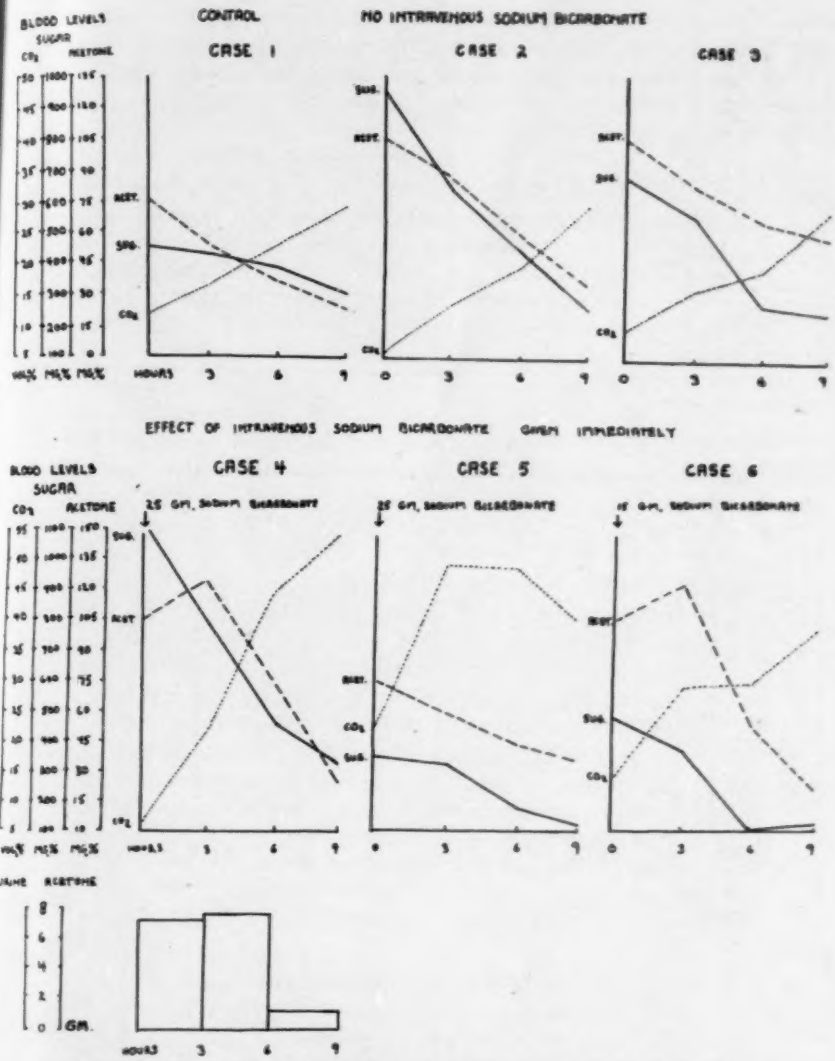



Fig. 1.—The effect of the intravenous administration of sodium bicarbonate on blood sugar, carbon dioxide-combining power and the level of acetone in the blood and urine. *Cases 1 to 3,* sodium bicarbonate not administered. *Cases 4 to 6,* sodium bicarbonate administered intravenously at the beginning of the nine hour period of observation.

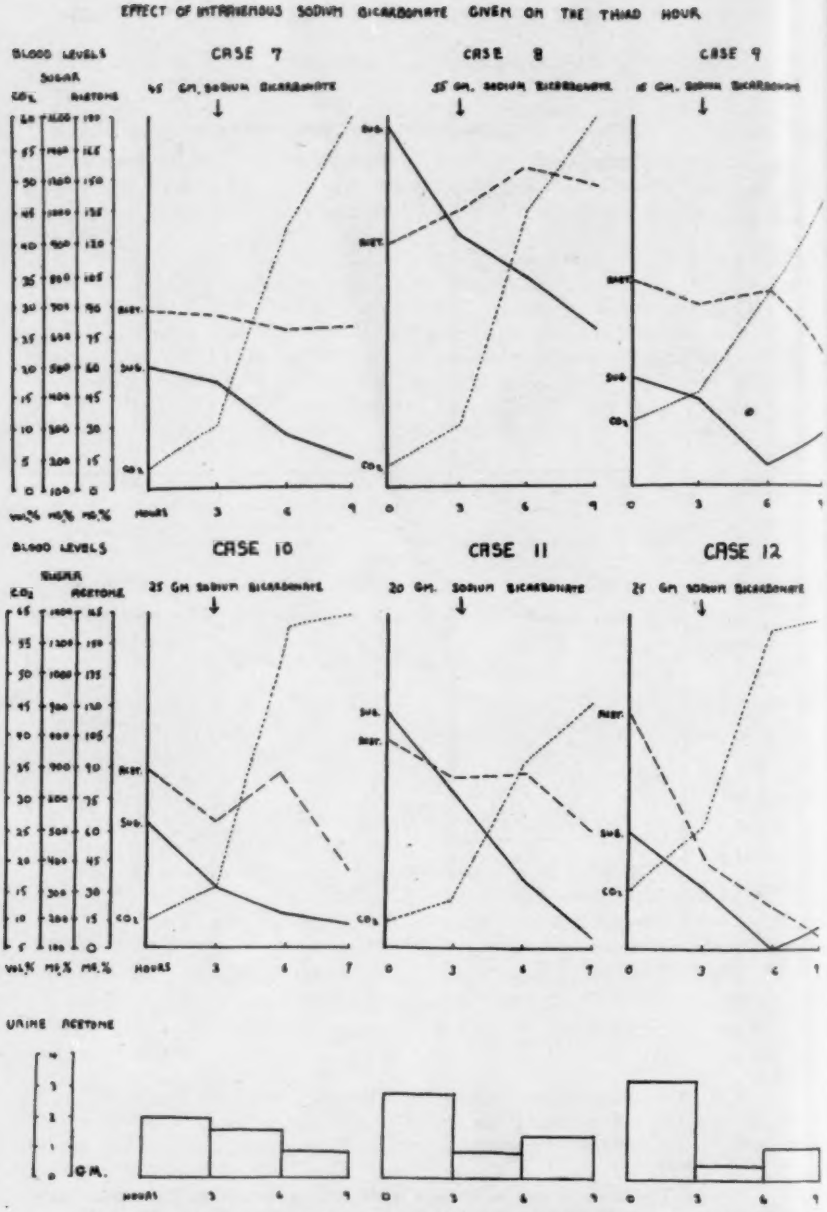



Fig. 2 (cases 7 to 12).—The effect of the intravenous administration of sodium bicarbonate at the third hour of a nine hour period of observation of the changes in blood sugar, carbon dioxide–combining power and the level of acetone in the blood and urine.

## RESULTS AND COMMENT

In the 3 control cases, in which no intravenous treatment with sodium bicarbonate was given, the carbon dioxide–combining power rose progressively during the nine hours of study after admission to the hospital. In 2 cases the rise was 15 volumes per cent, and in 1 case it was 23 volumes per cent (fig. 1, cases 1, 2 and 3). In the control cases the ketones in the blood fell progressively in inverse proportion to the rise of carbon dioxide–combining power.

The average rise of carbon dioxide–combining power in the 9 cases in which sodium bicarbonate was given intravenously, in doses varying from 15 to 55 Gm., was over twice as great as in the controls, but the results were not consistent. Whereas in 4 cases the maximal rise was 60 to 65 volumes per cent, in 2 cases the rise was no greater than that in the controls. Elevation of the carbon dioxide–combining power produced no effect on the mental state, the blood pressure, the output of urine or any other vital sign, but Kussmaul respirations were relieved with great consistency. This last-named effect is interesting, since the physiology of air hunger in diabetic ketosis has never been adequately explained. Although hyperventilation has been observed after the administration of ketone bodies containing the enol complex,[7] most workers agree that a lowered $p_H$ and carbon dioxide–combining power of the serum act directly on the respiratory center. We feel that the latter explanation is more correct. Kussmaul respirations were relieved immediately after administration of sodium bicarbonate, after the $p_H$ and carbon dioxide–combining power had been corrected but before any appreciable drop in the level of ketones in the blood was observed.

The effect of intravenous administration of sodium bicarbonate on the level of ketones in the blood was unexpected. In two thirds of the cases the ketones increased during the three hours following intravenous administration of sodium bicarbonate. The greatest rise (23 mg. per hundred cubic centimeters) occurred in a case of extremely severe ketosis in which a large amount of sodium bicarbonate was given (fig. 2, case 8). In 2 cases the increase was small but definite enough to be significant (fig. 2, cases 9 and 11). In one third of the cases the level of ketones in the blood failed to rise; the rate of fall was slower than that in the control cases.

The total output of ketones in the urine was measured in 4 cases in which sodium bicarbonate was given intravenously. In 3 cases the excretion of ketones in the urine was less immediately after the administration of sodium bicarbonate than during the subsequent three hours (fig. 1, case 4, and fig. 2, cases 11 and 12). This decrease is doubly significant, because in 2 of the 3 cases an increase in the ketones in the blood

7. Wright, S.: Applied Physiology, New York, Oxford University Press, 1937, p. 572.

occurred concomitantly with a lessened amount in the urine. Although in the fourth case the ketones in the blood increased after sodium bicarbonate was given, the amount in the urine fell progressively (fig. 2, case 10).

This rise in blood ketones and fall in urinary ketones immediately following the intravenous administration of bicarbonate is interesting. Sodium bicarbonate might accelerate the breakdown of fatty acids or liberate ketones from the tissues, but if this were true, one would expect an increased rather than a decreased amount of ketones in the urine. This divergence of the levels of ketones in the blood and the urine following administration of an alkali must indicate that the changes are due to a transitory decrease in elimination rather than to increased production of ketones. In any case, it seems safe to say that intravenous administration of sodium bicarbonate has no antiketogenic action in cases of diabetic ketosis and that it does not facilitate the elimination of ketones that have already accumulated in the blood and urine.

Study of the mortality rates for 154 cases of severe diabetic ketosis has likewise failed to show any benefit from sodium bicarbonate therapy.

One difficulty in evaluating any single therapeutic factor in diabetic ketosis by the case study method has been the great variation in the severity of disease in individual cases. Mortality statistics are of little comparative value when one clinic studies a group of unconscious patients who have infection or arteriosclerosis and another studies semiconscious patients in whom ketosis is not complicated by any other serious factor. When a clinical yardstick, such as Rabinowitch's classification, is used to estimate the severity of disease, much more significant comparisons can be made.

In 47 of the 154 cases of diabetes with associated ketosis in which adequate data were available, 10 Gm. or more of sodium bicarbonate was given intravenously within the first twenty-four hours of treatment. So few deaths occurred in the cases of mild ketosis that the figures are of little comparative value. The mortality for cases of moderately severe ketosis in which sodium bicarbonate therapy was given was slightly higher than that for those in which this treatment was not employed (40 per cent, as compared with 33 per cent). The mortality for control cases of severe ketosis was about the same as that for cases in which treatment was given (table). In general, the mortality was strikingly similar for the two groups of cases.

## SUMMARY

Twelve cases of diabetic ketosis were studied to determine the effect of intravenous administration of sodium bicarbonate on the level of blood sugar, carbon dioxide–combining power and the level of ketones in the blood and urine early in the period of treatment.

Intravenous injection of sodium bicarbonate raised the carbon dioxide-combining power and relieved Kussmaul respirations but was without effect on the level of sugar in the blood. No antiketogenic action was observed, but rather a slight tendency in some patients for the elimination of ketones to be delayed.

One hundred and fifty-four cases of diabetic ketosis, in approximately one third of which sodium bicarbonate was administered, were classified into five groups according to the intensity of the ketosis. The mortality rates both for the cases in which treatment was given and for control cases were determined.

If the severity of diabetic ketosis is taken into proper consideration in each case, there seems to be no difference in mortality between those cases in which treatment was with sodium bicarbonate and those in which no alkali was given.

There seems to be no practical basis for sodium bicarbonate therapy in the treatment of diabetic ketosis.

This study constitutes a part of the activities supported by the Espy Fund for Research in Diabetes.

Dr. C. A. Mills gave constructive advice and criticism during the course of the study and the preparation of the manuscript.

# RHEUMATIC PNEUMONIA

EMANUEL Z. EPSTEIN, M.D.
AND
EDWARD B. GREENSPAN, M.D.
NEW YORK

The occurrence of various pulmonary symptoms and signs in the course of acute and recurrent rheumatic fever has always perplexed clinicians. It is only natural that many writers should attribute them to a specific rheumatic infection. This specificity for the pulmonary changes has been accepted by some clinicians as a corollary to the pathologic alterations in other parts of the body occurring in rheumatic fever.

To Stoll,[1] is given the credit for first speaking of "rheumatic pleurisy" and "rheumatic peripneumonia," in 1788. Years later, in 1813, Chomel [2] mentioned pulmonary rheumatism. The real impetus to the problem was given by Latham,[3] in 1845, and Fuller,[4] in 1854. Latham, in a prophetic vein, wrote: "Such forms of pulmonary inflammation are portentous ingredients in the clinical history of acute rheumatism, and give a fearful interest to it," and Fuller went even further by claiming that "the pulmonary inflammation is due to the same cause of irritation, the same morbific agent which excites the articular and cardiac affections." For over eighty-five years the clinical and pathologic statistics of Latham and Fuller have been repeatedly cited, and over this same period names of many pathologists and clinicians have been added to the roster of supporters of the theory of the specificity of the pulmonary lesions occurring in acute rheumatic fever.

Ormerod,[5] in 1858, maintained that pneumonia constituted a regular part of "these two diseases, rheumatism and continued fever." In a

---

From the laboratories and wards of the Mount Sinai Hospital.

1. Stoll, M.: Rationis medeni, Vienna, 1788.

2. Chomel, A. F.: Essai sur le rhumatisme, Thesis, Paris, no. 63, 1813.

3. Latham, P. M.: Lectures on Subjects Connected with Clinical Medicine, Comprising Diseases of the Heart, London, Longmann [and others], 1845, vol. 1, pp. 159-179.

4. Fuller, H. W.: On Rheumatism, Rheumatic Gout, and Sciatica, New York, S. S. & W. Wood, 1854, pp. 249-256.

5. Ormerod, E. L.: Observations on Certain Forms of Disease of the Lungs, Brit. M. J., 1858, pp. 1025-1028.

similar vein wrote Howard [6] in 1885, Cheadle [7] in 1888 and Garrod [8] in 1890. Garrod said:

> In a considerable number of cases of rheumatic fever, inflammatory lesions of the lungs or pleura are observed; far less commonly, it is true, than endocarditis or pericarditis, but still with sufficient frequency to justify their inclusion among the more important accidents of the rheumatic state.

He expressed the opinion that the inflammatory lesion was a specific rheumatic pneumonia.

In the present century the question of the specificity of rheumatic pleurisy seems to have been answered in the affirmative by the work of Mosler,[9] of Rolly [10] (who found pleuritis in 2.4 per cent of 3,620 cases and who wrote that "diseases of the serous membranes are to be considered not as complications but rather as characteristics of the rheumatic disease, caused by the same cause as the acute articular rheumatism"), of Swift [11] (who found pleurisy in about 10 per cent of his patients with acute rheumatic fever) and of Paul [12] (who said: "It is questionable whether pleurisy should be regarded as a complication rather than another manifestation of rheumatic disease of the serous membranes of which pericarditis, pleurisy and even peritonitis are examples.").

The unanimity of opinion which existed in the past century in regard to rheumatic pneumonia and exists today in regard to rheumatic pleurisy is absent when the problem of the pneumonic complications in acute rheumatic fever is brought forward. There is agreement that varied pulmonary symptoms and signs are constantly encountered during the course of rheumatic fever, and the clinical descriptions have been ably presented by Coombs,[13] Rabinowitz,[14] Findlay,[15] Coburn [16] and others.

---

6. Howard, R. P.: Rheumatism, in Pepper, W.: A System of Practical Medicine by American Authors, Philadelphia, Lea Bros. & Co., 1885, vol. 2, pp. 19-69.

7. Cheadle, W. B.: Clinical Lecture on an Outbreak of Rheumatic Pneumonia, Lancet **1**:861-863, 1888.

8. Garrod, A. E.: A Treatise on Rheumatism and Rheumatoid Arthritis, Philadelphia, P. Blakiston, Son & Co., 1890, chap. 11, pp. 105-111.

9. Mosler, E.: Ueber rheumatische Entzündung der serösen Häute (sogenannte Polyserositis rheumatica), Berl. klin. Wchnschr. **47**:277-279, 1910.

10. Rolly, F.: Der akute Gelenkrheumatismus, Berlin, Julius Springer, 1920.

11. Swift, H. F.: Rheumatic Fever, (*a*) in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1930, vol. 1, p. 401; (*b*) in Cecil, R. L.: Textbook of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1937.

12. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine **7**:383-410, 1928.

13. Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood and Company, 1924.

14. Rabinowitz, M. A.: Rheumatic Pneumonia, J. A. M. A. **87**:142-144 (July 17) 1926.

*(Footnotes continued on next page)*

The onset is insidious during the course of active rheumatic fever, usually without evidences of congestive heart failure. The customary signs and symptoms of ordinary pneumonias, such as symptoms referable to the upper respiratory tract, chill, chest pain and rusty sputum, are absent. The physical signs are usually observed at the bases of one or both lungs, although they are frequently present in the upper lobes. There may be the characteristic signs of consolidation or only scattered rales and diminished breathing. The signs of resolution frequently seen in pneumonia are generally absent. The rapid disappearance of symptoms within a few days and the migratory and fleeting character of the consolidation, with rapid involvement of other sites, distinguish the clinical picture from that of lobar pneumonia or bronchopneumonia, usually encountered. The roentgenograms are interpreted as characteristic of one of the following conditions: intense congestion, edema, pneumonitis or infiltration, infarct or pneumonia.

The recent intensive pathologic restudy of the pulmonary changes occurring in rheumatic fever can be considered to have started with the report of Paul, who found in 30 cases that "in more than half there were evidences of a focal hemorrhagic lesion, rather widespread, involving individual lobules or groups of lobules, which might be interpreted as an early or hemorrhagic stage of a broncho- or lobular pneumonia." He expressed the belief that sufficient evidence had not been accumulated to prove this lesion to be a specific manifestation of rheumatic fever, although it seemed to be a fairly characteristic finding.

At about the same time Naish [17] described what he called a new type of pathologic consolidation of the lung in rheumatic fever and termed the condition "rheumatic lung." He was impressed by the characteristic macroscopic appearance of the affected parts, which was unlike that seen in any other form of pneumonia. The consistency was not unlike that of solid india rubber, very tough and nonfriable. The color was a shade of purplish red, homogeneous in tint on section. The most striking microscopic feature was an enormous endothelial proliferation, the cells apparently originating from the walls of the alveolar capillaries. Naish expressed the belief that the reactive process was identical with that described by Coombs as pathognomonic of rheumatic infection elsewhere in the body.

Even more emphatic about the specificity of rheumatic pneumonia was Fraser's [18] report. In 2 cases of acute rheumatic fever he found the

15. Findlay, L.: Pulmonary Lesions in Rheumatism, Arch. Dis. Childhood **5**:259-264, 1930.

16. Coburn, A. F.: The Factor of Infection in the Rheumatic State, Baltimore, Williams & Wilkins Company, 1931.

17. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10-14, 1928.

18. Fraser, A. D.: The Aschoff Nodule in Rheumatic Pneumonia, Lancet **1**: 70-72, 1930.

pulmonary lesion in its acute stage characterized by vascular changes and proliferation and later by necrosis of alveolar cells and destruction of bronchi. It resembled an acute interstitial pneumonia. Fraser found what he considered to be typical Aschoff nodules in the interstitial tissue of the lung, most prominent in the interlobular septums.

Coburn [19] found the changes in the lungs in rheumatic fever to consist of: subpleural and alveolar hemorrhage, with engorgement of the blood vessels; interstitial and alveolar edema; infiltration by wandering cells, with resultant massive accumulation of large mononuclear cells in clusters; round cells and, rarely, polymorphonuclear cells; deposition of a hyaline membrane along the walls of the alveolar sacs, and the absence of detectable micro-organisms in the affected areas. These lesions, like those in the skin, brain, kidneys and abdominal viscera, suggested alteration in vascular permeability with diapedesis and damage to the mesodermal tissues, accompanied in certain instances by inflammatory reaction. Coburn observed 45 instances of hemorrhagic pulmonary solidification among the 320 cases studied. He did not observe specific histologic structures (Aschoff bodies). In his book, Coburn [16] stated, "The histological lesions regarded as specific in rheumatic disease have not been defined in the lung. This is believed due to the character of the tissue developing the rheumatic process."

Similarly, Klinge,[20] who had a most extensive experience with rheumatic fever, did not consider the pulmonary lesions as characteristic or specific. He noted, as did Paul, and also Coburn, inflammatory lesions with hemorrhagic foci and found difficulty in differentiating the roles played by chronic stasis and rheumatic inflammation in their pathogenesis. He never saw Aschoff bodies in the lung, although he observed the Aschoff nodules described by Fraser in the adventitia of the pulmonary artery. Similar nonspecificity was observed by Cook [21] and Melnick.[22]

Gouley and Eiman,[23] like Naish and Fraser, have emphasized in repeated communications the specificity of the lesions found in the lungs in rheumatic fever. They noted that the inflammatory pulmonary reaction

19. Coburn, A. F.: Relationship of the Rheumatic Process to the Development of Alterations in Tissues, Am. J. Dis. Child. **45**:933-972 (May) 1933.

20. Klinge, F.: Das Gewebsbild des fieberhaften Rheumatismus, Virchows Arch. f. path. Anat. **286**:344-388, 1932.

21. Cook, G. T.: On the Association of Pulmonary Changes with Rheumatic Pericarditis, Brit. J. Child. Dis. **29**:264-276, 1932.

22. Melnick, P. J.: Pulmonary Changes in Rheumatic Fever, Illinois M. J. **73**:336-339, 1938.

23. Gouley, B. A., and Eiman, J.: The Pathology of Rheumatic Pneumonia, Am. J. M. Sc. **183**:359-381, 1932.

consisted of an interstitial perivascular exudate of large endothelial cells, identical morphologically with those found in lesions in the heart caused by rheumatic fever and considered pathognomonic of that disease. They concluded by saying, "We therefore consider that in many virulent cases a characteristic rheumatic pneumonia is to be found." Likewise, Lutembacher [24] claimed the existence of a rheumatic pneumonia, which was characterized grossly by homogeneous areas of hepatization and microscopically by leukocytic alveolitis without fibrinous exudate and by a marked hemorrhagic edema and exudative lesion in the alveoli.

The most provocative contributions to the already long list have been added recently by Masson, Riopelle and Martin [25] and Hadfield.[26] The former studied 13 cases of rapidly fatal, active rheumatic fever, all but 1 of which were in infants, with Aschoff bodies present in the heart in all cases. The outstanding changes were: (*a*) alveolitis, which was edematous, catarrhal, serofibrinous or fibrinohemorrhagic in character, with a seroalbuminous alveolar exudate, poor in fibrin and blood elements, but filled with alveolar cells; (*b*) hyaline membranes in the terminal bronchioles in 10 of the 13 cases, and (*c*) a proliferative, fibroblastic interstitial lesion. No Aschoff bodies were found in the lungs. Masson, Riopelle and Martin concluded:

> To our knowledge, the pneumopathy which we have just described is particular to young persons with rheumatic fever. Without a doubt, Aschoff bodies, the "signature" of rheumatic fever, do not occur in this condition, and the primary lesions which constitute the pneumopathy are not strictly exclusive. But their extreme frequency in the course of infantile rheumatism, their combination, their extension and their anatomic features contribute to the individuality of the pathologic picture.

Hadfield recently reported 5 cases of the acute stage of rheumatic fever in young people and recorded changes similar to those described by Masson. Hadfield described the primary lesion as widespread fibrinous alveolitis, followed by an infiltration of mononuclear cells, which developed slowly but eventually became copious and diffuse. In cases with a fatal outcome this primary lesion was complicated by formation of a hyaline pseudomembrane in most of the alveolar ducts in the consolidated lung. This process occurred in the finest ramifications of the airways in the presence of a viscid albuminous exudate and a period of severe insipiratory dyspnea.

---

24. Lutembacher, R.: Congestion suraigüe oedémateuse du poumon dans la maladie de Bouillaud, Rev. du rhumatisme **3**:257-274, 1936.

25. Masson, P.; Riopelle, J. L., and Martin, P.: Poumon rhumatismal, Ann. d'anat. path. **14**:359-382, 1937.

26. Hadfield, G.: The Rheumatic Lung, Lancet **2**:710-712, 1938.

We have studied the problem of the pulmonary changes in rheumatic fever from a different aspect, choosing our cases in consecutive order, eliminating none of them because of the absence of clinical or macroscopic evidences of pneumonia or consolidation. In this manner we believe the evolution of the entire pulmonary picture may be unfolded in chronologic sequence and the histologic changes correlated with the approximate duration of the disease as determined from the clinical history. Toward this end we have ascertained the duration of the illness at home before admission to the hospital, the time spent in the institution before death and the number of previous attacks of rheumatic fever, as well as the presence of chronic valvular changes from the preceding attacks. This has enabled us to study the pathologic changes in the lung in relation to the acuteness and the duration of the rheumatic fever.

Forty-five cases of acute rheumatic heart disease were studied at autopsy and were divided into three groups on the following basis: (1) absence of a previous history of rheumatic fever, no evidence of chronic valvular disease and an acute, rapidly fatal initial attack, (2) a previous history of rheumatic fever, evidence of chronic valvular disease and a rapidly fatal course in the last admission, and (3) chronic rheumatic cardiovalvular disease with the fatal attack lasting a considerable time.

GROUP 1

This group includes 14 cases in which the patient died during the first attack of acute rheumatic fever. The ages of the patients varied from 19 months to 25 years; 7 were below 5 years of age, 2 were between 5 and 10, 3 were between 10 and 20, 1 was 22 and 1 was 25. The entire stay in the hospital, from admission to death ranged from a few hours to six weeks. Two patients died a few hours after admission; 3 died in one day, 2 in two days, 2 in five days and 1 each in six, seven, ten, twenty and forty-two days.

The earliest lesion in the lungs in acute rheumatic fever was observed in the case of a boy 7 years old who had had no previous attack, who had been ill only a short time and who died as he entered the hospital admitting room, before he could be sent to the ward. No chronic valvular disease was observed at autopsy, but acute verrucous endocarditis of all valves, acute fibrinous pericarditis and rheumatic myocarditis, with many Aschoff bodies, were found. The striking histologic alterations in the lungs were the marked edema and severe congestion with areas of hemorrhage. The alveoli were filled with desquamated epithelial cells with large nuclei and clear pale cytoplasm. The edema fluid did not show any fibrin. A striking feature was the presence of hyaline eosinophilic bands along the respiratory bronchioles and alveolar ducts. This

hyaline material did not stain for fibrin, contained fat, was not doubly refractile and stained yellowish orange with sudan, deep red with Mallory's aniline blue acid fuchsin and vermilion–purplish red with phosphotungstic acid hematoxylin. The arteries, arterioles, veins and bronchi were normal. A similar opportunity to study an early pulmonary lesion occurred in the case of an infant of 19 months who died after one day in the hospital. The lungs were firm and fleshy, and only a few aerated patches could be detected. There were marked congestion, edema and desquamation of epithelial cells into the alveoli, which were literally bulging with edema fluid, desquamated cells and erythrocytes. The

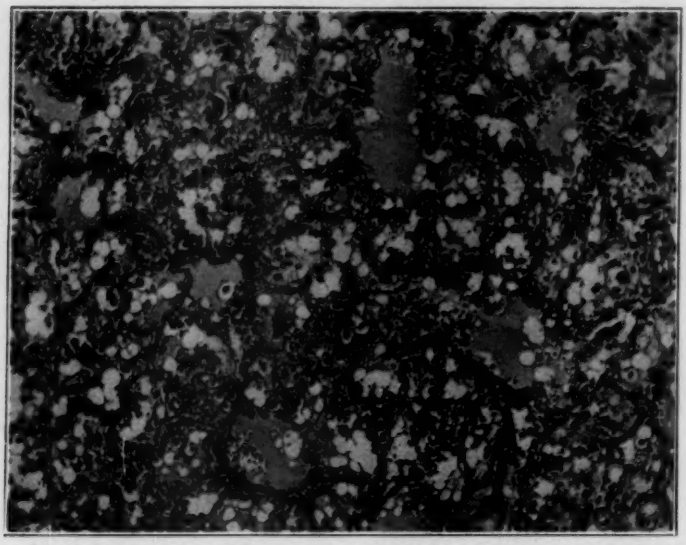


Fig. 1.—A section of the lung of a 4 year old child who died during the first attack of rheumatic fever after only two days in the hospital. The alveoli are filled with edema fluid, erythrocytes and numerous mononuclear cells. Note the striking hyaline bands (*A*) along the walls of the respiratory bronchioles.

edema fluid extended into the septal walls and interlobular septums. The respiratory bronchioles were filled with hyaline eosinophilic bands.

From 2 cases in which the patients died within a week after the onset of the attack of rheumatic fever, we deduced further steps in the sequence of events. In addition to the features just mentioned the alveolar septums had become moderately thickened and edematous and in many areas contained large mononuclear cells in their stroma. The large mononuclear epithelial cells desquamated into the alveoli already

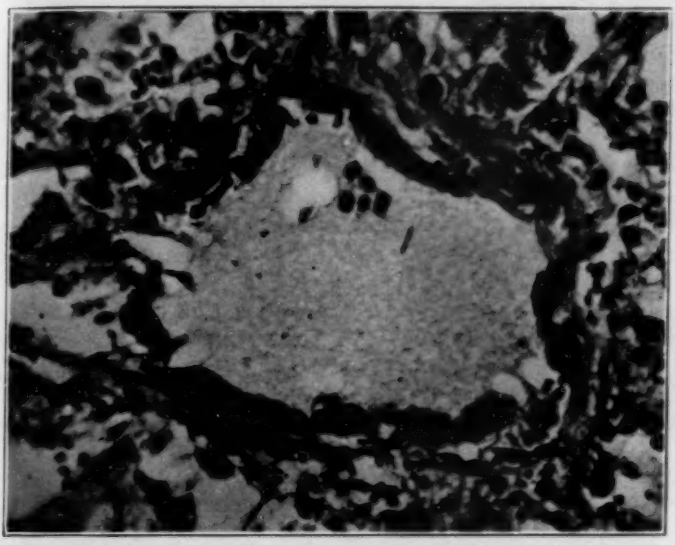


Fig. 2.—High power magnification of the hyaline bands marked *A* in figure 1.

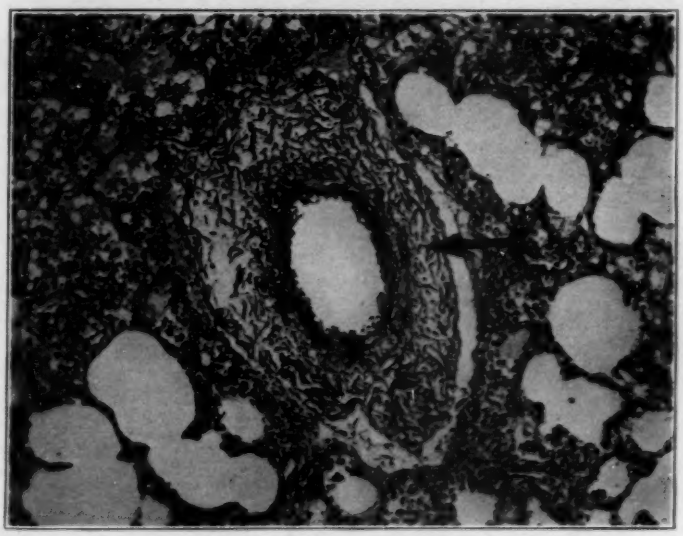


Fig. 3.—Periarterial edema in the lung of the child referred to in figure 1.

showed phagocytosis of erythrocytes and, in some areas portions of the hyaline membranes. Hyaline thrombi occurred frequently in the alveolar capillaries. In cases in which autopsy was done after the second or third week of illness, the subpleural areas were observed to contain an infiltration of mononuclear cells. In some sections there were definite areas of fibrosis and various stages of organization. The arteries had already become thickened with increased periadventitial tissue, which in some instances had undergone fibrinoid degeneration. Occasionally small arteries were seen to be occluded by thrombi.

From the study of the foregoing 14 cases in which the patients died in the initial attack of rheumatic fever and in which there were no complications of stasis due to previous cardiovalvular disease, one may reconstruct the chronologic change in the lungs as follows: (1) considerable edema, first intra-alveolar, then septal and interlobular; (2) congestion of alveolar capillaries and diapedesis of erythrocytes in large numbers into the alveoli; (3) desquamation into the alveoli of large mononuclear cells, which later showed phagocytosis; (4) formation of hyaline membranes in the respiratory bronchioles and alveolar ducts in 50 per cent of the cases; (5) beginning thickening and infiltration of the interlobular septums with mononuclear cells, beginning fibrosis and organization, and (6) thickening of smaller arteries and occasional occurrence of hyaline thrombi in them. Grossly the lungs showed patchy foci of dark red, fleshy, noncrepitant, nonaerated areas.

This study of the chronologic development of pulmonary changes was continued in the remaining 31 cases of acute rheumatic fever, in which one or more previous attacks had resulted in chronic cardiovalvular disease of the mitral, aortic or tricuspid valve. These cases were divided according to the duration of the fatal attack of rheumatic fever before autopsy, with death occurring three weeks, six weeks or longer than six weeks after the onset of the illness.

### GROUP 2

*Subgroup A.*—In 10 cases of previous rheumatic cardiovalvular disease death occurred within three weeks after the onset of the fatal attack. The ages of the patients ranged from 7 to 38 years. It is difficult to state definitely how many previous attacks had occurred in each case; in 4, however, a history of only one previous attack was obtained. Disease of the mitral valve was present in all cases; in addition the aortic valve was involved in 7 cases and the tricuspid in 3. Aschoff bodies occurred in 8 cases and acute fibrinous pericarditis in 3 cases.

In 3 of these 10 cases the histologic picture encountered in the preceding group was observed, namely, alveoli everywhere filled with edema fluid, erythrocytes and medium and large desquamated epithelial

cells; extreme congestion of the alveolar capillaries, and hyaline membranes outlining the respiratory ducts. In addition, in these 3 cases, the epithelial cells had already undergone fragmentation and exhibited phagocytosis of erythrocytes and pigment.

In the other 7 cases the evolution of the pathologic process in the lung tended to run thus: Beneath the thickened pleura were areas of fibrosis and pseudogland formation suggesting regeneration of alveolar epithelium, large areas of atelectasis with thickened alveolar septums and congestion, chronic edema and numerous clumps of pigment-laden macrophages and epithelial cells showing erythrophagocytosis. There were scattered emphysematous alveoli, intimal hyperplasia and medial thickening of the medium-sized and larger pulmonary arteries, areas of organization and carnification, thickening of the interalveolar septums, and thrombi in some of the smaller arteries.

In 5 of the 10 cases pneumonia was present at death. In 1 case the exudate was predominantly hemorrhagic; in the others the usual picture of confluent bronchopneumonia was present, with polymorphonuclear leukocytes, erythrocytes, fibrin, etc.

*Subgroup B.*—In 11 cases one or more previous attacks of rheumatic fever, with subsequent chronic cardiovalvular disease, occurred and the final fatal attack lasted up to six weeks from the onset of symptoms to death. The ages ranged from 3 to 45 years. A defect of the mitral valve occurred in every case, together with a defect of the aortic valve in 6 cases, of the tricuspid valve in 5 cases and of the pulmonary valve in 1 case; fibrinous pericarditis was present in 6 cases, and Aschoff bodies were seen in 7 cases. In these 11 cases we were impressed by the chronic character of the pulmonary changes. The pleura was thickened and vascularized, and the subpleural area showed an increase in lymphocytes. The alveoli were more frequently collapsed than in the preceding group, and their walls were thickened and in places completely obliterated. The walls of the alveolar septums were markedly thickened. We observed increased numbers of heart failure cells, desquamated epithelial cells containing erythrocytes; thickened and congested alveolar capillaries; thickened arteries with perivascular fibrinoid degeneration and vacuolation of the media; thrombi with infarctions, areas of atelectasis and collapse, and scattered areas of pneumonia. Bronchopneumonia occurred in 5 cases, and the infiltration was characteristically peribronchial, with polymorphonuclear leukocytes, fibrin and bacteria, and with polymorphonuclear exudate in the bronchi and occasional destruction of the bronchial wall.

In 4 cases of this group, those of patients aged 3, 6, 13 and 14, with a history of fairly acute disease and the presence of Aschoff bodies and fibrinous pericarditis, there occurred a reaction similar in some respects to that seen in the first group, in which the initial attack of rheumatic

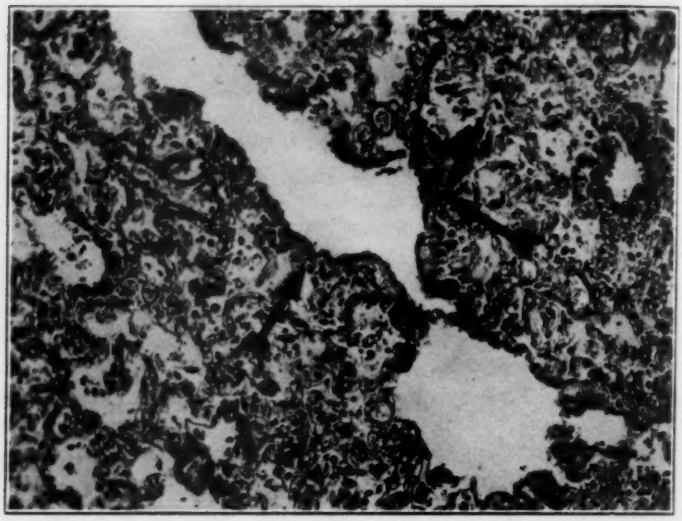


Fig. 4.—Hyaline membranes in the respiratory bronchioles in the lung of a 4 year old child who died during the first attack of rheumatic fever after ten days in the hospital.

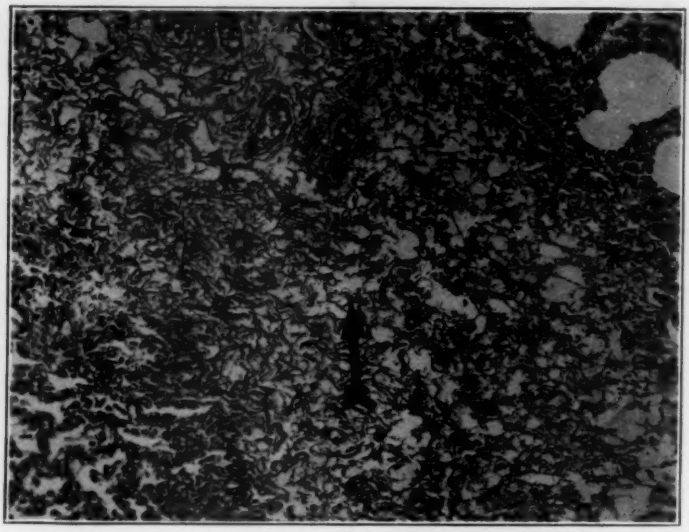


Fig. 5.—Striking widening of the interlobular septum of the lung due to edema in the case of the child referred to in figure 4.

fever was fatal. We observed marked congestion, diapedesis of erythrocytes into alveoli, transudation of edema fluid into alveoli and alveolar septums, congestion of alveolar capillaries, desquamation of epithelial cells into alveoli and hyaline membranes outlining the respiratory bronchioles and alveolar ducts. In only 1 of these 4 cases were there also the marked chronic stages seen in the others.

GROUP 3

The last group studied comprised 10 cases in which there had been at least one previous attack of rheumatic fever and in which the

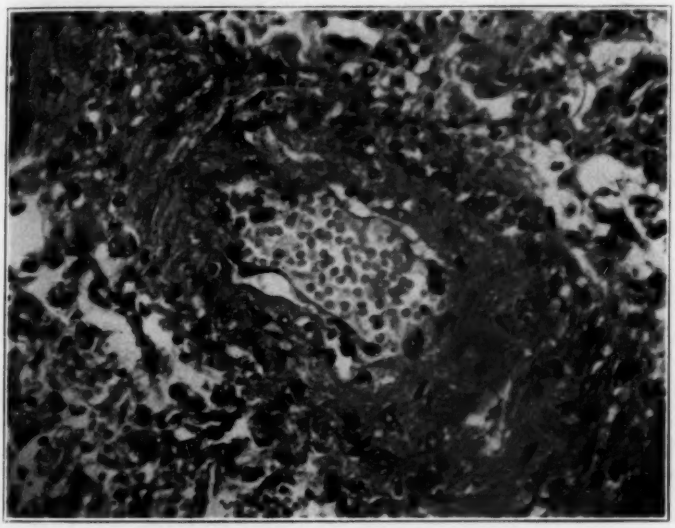


Fig. 6.—A section of the pulmonary artery of a 17 year old patient with chronic rheumatic cardiovalvular disease who died during an attack of acute rheumatic fever two months after admission to the hospital. The wall of the artery shows marked necrosis, and an adventitial and periarterial inflammatory reaction is evident.

total duration of the final fatal attack had been longer than six weeks. The chronic cardiovalvular lesion affected the mitral valve in 9 cases; in 5 of these the aortic valve, in 4 the tricuspid valve, was also involved. In 1 case the aortic valve alone was affected. Fibrinous pericarditis was present in 4 instances and Aschoff bodies in 6 instances. The ages of the patients ranged from 12 to 51 years.

Here we encountered the picture mainly of organization and fibrosis. In only a few instances did we see the acute phase of congestion, edema

and desquamation of epithelial cells into the alveoli. The common lesion consisted of atelectasis and collapse, with areas of interstitial fibrosis; formation of new blood vessels; marked thickening of the alveolar septums; organization of the alveolar exudate; destruction of alveolar structure by wide bands of connective tissue; large numbers of heart failure cells; peribronchial thickening; hypertrophy of the musculature of the respiratory bronchioles; occlusion of the pulmonary arteries by thrombi; marked intimal proliferation and narrowing of the arteries and arterioles, going on to complete obliteration, and perivascular infiltration and thickening of the media. In 2 cases hyaline membranes lined the respiratory bronchioles and the alveolar ducts. In 5 cases there occurred patchy bronchopneumonia of various lobes, which was no different than the usual bacterial pneumonias seen as complications of any other chronic disease.

### CONTROL GROUPS

In order to eliminate the possibility that the lesions which we have described in the lungs in cases of acute rheumatic fever might have occurred as a result of congestive heart failure, we studied the following groups of controls: 20 cases of chronic rheumatic cardiovalvular disease, mitral stenosis, in which the patient died of another disease or of chronic heart failure without any evidences of acute rheumatic fever; 23 cases of acute and chronic disease of the coronary arteries in which death was due to heart failure, and 16 cases of hypertension, either essential or malignant or due to chronic glomerulonephritis, with cardiac failure.

In none of the 20 cases of mitral stenosis in which death was due to another, unrelated disease or to chronic cardiac failure without acute rheumatic fever did we observe the hyaline membranes that we have seen to be conspicuous in many cases of acute rheumatic fever. We did find the chronic condition in the lungs described in the cases in which previous rheumatic attacks had occurred and in which death had terminated an acute phase of rheumatic fever lasting for several weeks. The lungs in these 20 control cases presented chronic congestion and edema, numerous heart failure cells, intra-alveolar fibrosis, fibroblastic proliferation, organization of alveolar exudate, thickening of the pleura with vascularization, atelectasis with carnification, thickened alveolar septums, thickening of arteries and arterioles, multiple infarcts, septal thickenings, emphysema and patchy areas of ordinary terminal bacterial bronchopneumonia.

There was no evidence of hyaline membranes in the lungs in the 23 control cases of acute and chronic coronary arterial disease in which death was due to cardiac failure, and the only changes in the lungs were chronic ones characteristic of long-standing pulmonary congestion.

In the 16 control cases of hypertensive heart disease with failure the picture was similar to that just described. In 1 case, that of a patient aged 23 who died in uremia of chronic glomerulonephritis with hypertensive cardiac disease and mild failure, we found hyaline membranes lining the respiratory ducts, similar in appearance to those occurring in the cases of acute rheumatic fever.

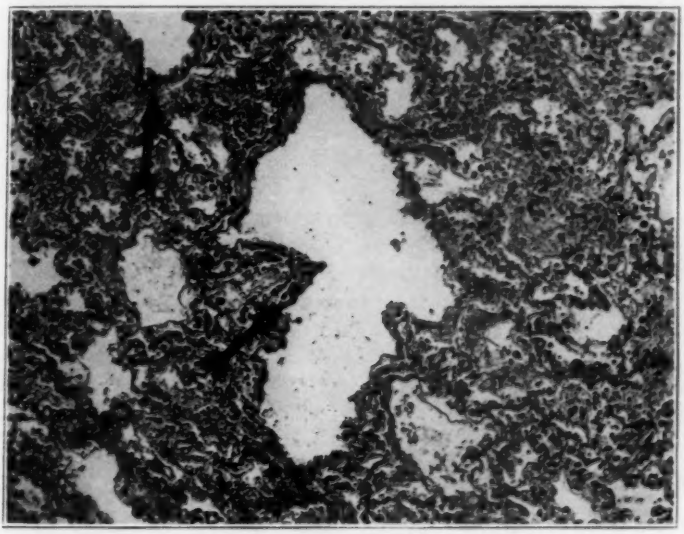


Fig. 7.—Hyaline bands along the walls of the respiratory bronchioles of a 23 year old patient with chronic glomerulonephritis who died in uremia. These bands are similar to those occurring in the lungs in cases of acute rheumatic fever.

## HYALINE MEMBRANES IN THE LUNGS

Before entering on a discussion of the occurrence and pathogenesis of hyaline membranes in the lungs it is necessary to study briefly the anatomy of the bronchial tree. In their book on epidemic respiratory disease, Opie, Blake, Small and Rivers [27] have given this description:

It is convenient to designate as respiratory bronchioles the terminal ramifications of the bronchi; they are lined by a single layer of columnar ciliated cells passing over into cuboidal non-ciliated epithelium and are beset with small air sacs lined

27. Opie, E. L.; Blake, F. G.; Small, J. C., and Rivers, T. M.: Epidemic Respiratory Disease, St. Louis, C. V. Mosby Company, 1921.

by flat cells or epithelial plates similar to those of the alveoli elsewhere. The respiratory bronchiole by branching along its course or at its end is continued into several alveolar ducts which unlike the respiratory bronchioles have no cubical or columnar epithelium but are closely beset by alveoli lined by flat epithelial plates. The alveolar duct is recognized by the absence of cuboidal epithelium and the presence of bundles of smooth muscle which occur in the wall. The infundibula or alveolar sacs arise as branches from the alveolar ducts and like them are beset with alveoli but smooth muscle does not occur in their walls. The base of the infundibulum is wider than its orifice.

The formation of a layer of hyaline material on the inner surface of alveolar ducts and infundibula in epidemic influenza has been described by LeCount [28]; Goodpasture and Burnett [29]; Wolbach [30]; Klotz [31]; MacCallum [32]; Opie, Blake, Small and Rivers [27]; Wolbach and Frothingham [33]; Brannan and Goodpasture,[34] and Opie.[35] Klotz stated that this material had none of the staining reactions of fibrin and suggested it was made up of necrotic cells of the septum, which previously had suffered edema and circulatory interference. For a long time the occurrence of hyaline membranes in the lungs was considered characteristic of influenza.

Wolbach and Frothingham demonstrated, however, that the hyaline membrane in the alveolar ducts was an effect produced by air forced into exudate. They did not know of what the hyaline membrane was composed but expressed the opinion that it was related to the action of the air and the virus on some of the body fluid or exudates in epidemic influenza and not to degenerated epithelium. They based their conclusions on 2 cases in which the air had escaped from the lungs into the mediastinum with the development of the same hyaline membrane in the tissues of the mediastinum, where no epithelium existed. In both cases pneumococcic pericarditis and an acute infiltration of the fat and

28. LeCount, E. R.: The Pathologic Anatomy of Influenzal Bronchopneumonia, J. A. M. A. **72**:650-652 (March 1) 1919; Disseminated Necrosis of Pulmonary Capillaries in Influenzal Pneumonia, ibid. **72**:1519-1520, (May 24) 1919.

29. Goodpasture, E. W., and Burnett, F. L.: The Pathology of Pneumonia Accompanying Influenza, U. S. Nav. M. Bull. **13**:177-197, 1919.

30. Wolbach, S. B.: Comments on the Pathology and Bacteriology of Fatal Influenza, Bull. Johns Hopkins Hosp. **30**:104-109, 1919.

31. Klotz, O.: The Pathology of Epidemic Influenza, in Publications from the University of Pittsburgh School of Medicine, 1919, pp. 207-285.

32. MacCallum, W. G.: Pathology of the Pneumonia Following Influenza, J. A. M. A. **72**:720-723 (March 8) 1919.

33. Wolbach, S. B., and Frothingham, C.: The Influenza Epidemic at Camp Devens in 1918, Arch. Int. Med. **32**:571-600 (Oct.) 1923.

34. Brannan, D., and Goodpasture, E. W.: The Pathology of Pneumonia Caused by Bacillus Influenzae During an Interepidemic Period, Arch. Int. Med. **34**:739-756 (Dec.) 1924.

35. Opie, E. L.: The Pathologic Anatomy of Influenza, Arch. Path. **5**:285-304 (Feb.) 1928.

areolar tissue of the mediastinum were present. Air bubbles also penetrated the mediastinal tissues, and wherever the air came in contact with this exudate the hyaline membrane was found. They expressed the belief that the air must be under some tension in its contact with the exudate before the membrane could be formed.

Confirmation of this concept was then brought forward by Farber and Sweet,[36] who observed membranes lining the respiratory ducts and alveoli in fetuses in which death had been due to intrauterine asphyxia. The membranes had the appearance and staining reactions of vernix. It appeared to them that the greater and more prolonged the intrauterine asphyxia, with aspiration of the contents of the amniotic sac and resultant interference with later extrauterine respiration, the greater the size and number of membranes in the lungs.

And, finally, Farber and Wilson,[37] in an extensive study of human material and ingeniously conducted animal experiments, were able to establish definitely the nature and the pathogenesis of the hyaline membranes in the lungs. They found the hyaline membranes identical in influenzal pneumonia, in various types of pneumonia in infants and growing children and in the lungs of newborn infants after aspiration of the contents of the amniotic sac. These membranes stained from pink to red with hematoxylin and eosin and from salmon pink to red with phosphotungstic acid hematoxylin, contained varying amounts of fat and did not reveal fibrin when stained for this material.

When animals were forced to breathe an atmosphere of such low oxygen and high carbon dioxide content that marked dyspnea leading to death occurred, the alveolar spaces were filled with varying amounts of serum frequently pressed by the inspired air into membrane formation against the alveolar walls. Also, when a foreign substance, such as horse serum, india ink or fibrinopurulent exudate, was instilled into the trachea and vigorous artificial respiration (Drinker) instituted, characteristic membranes formed of the material could be found lining the alveolar walls. They therefore concluded that for the production of the characteristic hyaline membranes these factors were necessary: (1) material capable of taking the characteristic eosin stain; (2) air in the alveolar spaces, probably under greater than normal tension; (3) partial obstruction to the passage of the air by semifluid material in the air passages, and (4) dyspnea, which may be interpreted as violent inspiratory efforts to force air by this obstruction.

The hyaline membranes in the lungs in cases of acute rheumatic fever, observed by Coburn; by Masson, Riopelle and Martin; by Had-

36. Farber, S., and Sweet, L. K.: Amniotic Sac Contents in the Lungs of Infants, Am. J. Dis. Child. **42**:1372-1383 (Dec.) 1931.

37. Farber, S., and Wilson, J. L.: The Hyaline Membrane in the Lungs, Arch. Path. **14**:437-460 (Oct.) 1932.

field, and by us, must therefore be interpreted in the light of the studies just reviewed. Not only have the hyaline membranes been found in patients with influenzal or various other forms of pneumonia, in asphyxiated infants with aspirated contents of the amniotic sac and in experimental animals, but we have observed them also in the lungs in 1 case each of malignant nephrosclerosis with uremia and mild cardiac failure, metastatic carcinomatosis of the lung, Hodgkin's disease, lymphosarcomatosis and subacute bacterial endocarditis.

### ARTERIAL LESIONS

The early lesions in the lungs in cases of acute rheumatic fever—alveolitis, engorgement of capillaries, edema, congestion and the deposition of the hyaline membrane along the respiratory ducts—strongly suggest an alteration in the vascular permeability, with resultant diapedesis of red blood cells and transudation of an albuminous fluid into the alveoli. Vascular damage elsewhere in the body has been demonstrated in cases of acute rheumatic fever—in the skin, brain, kidneys and abdominal viscera; of especial interest in this connection are the changes observed in the main pulmonary artery and in its branches and ramifications in the lung.

Paul [38] was the first to observe extensive lesions in the media, with Aschoff bodies in the adventitia, of the pulmonary artery in a case of acute rheumatic fever. Kugel and Epstein,[39] in 24 cases of active rheumatic fever, found severe lesions, consisting of diffuse cellular infiltration in the intimal and subintimal layers of the media, with marked disruption of the elastic media, in the pulmonary artery in 5 instances. Von Glahn and Pappenheimer [40] had previously demonstrated changes in the smaller branches of the pulmonary artery.

In our series of 45 cases of acute rheumatic fever we have observed various changes in the smaller pulmonary arteries, arterioles and capillaries. Interestingly enough, in the 14 cases of acute, rapidly fatal rheumatic fever in which death occurred during the initial attack, no important or significant lesions were seen in the branches of the pulmonary artery. Severe arteritis was observed in 4 of the remaining 31 cases of acute fatal rheumatic fever with one or more previous attacks and resultant valvular changes. The lesions were severe, with perivascular, adventitial and medial infiltration of polymorphonuclear and

38. Paul, J. R.: Lesions in the Pulmonary Artery in Rheumatism, Arch. Path. **3**:354 (Feb.) 1927.

39. Kugel, M. A., and Epstein, E. Z.: Lesions in the Pulmonary Artery and Valve Associated with Rheumatic Cardiac Disease, Arch. Path. **6**:247-262 (Aug.) 1928.

40. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235-249, 1926.

mononuclear cells, destruction of the media and marked intimal infiltration and proliferation causing complete destruction of the vessels, which usually were the medium-sized arteries and arterioles. Otherwise, the usual vascular change in these cases was one of intimal proliferation (which progressed in many instances to complete obliteration of the lumen), distinct medial thickening and adventitial proliferation undergoing fibrinoid degeneration. Many of these medium-sized and smaller arteries and arterioles were occluded by thrombi. Occasionally the veins were seen to be thickened and hyperplastic.

### HEPATIC EDEMA

In order to throw further light on the probability of capillary damage in rheumatic fever, we have studied the liver in all 45 cases of acute rheumatic fever, as well as in the control cases. Rössle [41] has long looked on hepatic edema as the evidence of a toxic lesion of the capillary wall, which becomes permeable to plasma and suffers destruction and desquamation of its endothelium. Keschner and Klemperer [42] found 79 instances of intrahepatic edema in a series of 505 unselected autopsies (15 per cent), and intrahepatic edema was detectable in 39 per cent of cases of cardiac failure. They failed to find any difference in the frequency of the edema between the cases of failure during rheumatic fever and those of failure due to vascular myocardial lesions. For this reason they accounted for the hepatic edema on a mechanical basis. However, their finding of hepatic edema in cases of malignant nephrosclerosis, influenza, diabetic coma, uremia and exophthalmic goiter, without coexistent cardiac failure, led them to believe that primary hepatic edema is of significance as the only morphologic evidence of increased permeability of the capillary wall.

We have studied the livers according to the method outlined by Keschner and Klemperer and have regarded as showing edema only those sections in which the capillary walls were separated from the liver cell cords and in which the distended pericapillary (Disse) spaces contained stained granular (protein) material. Mere separation of the capillary wall was not accepted as evidence of edema, since focal detachment alone could be demonstrated in almost every instance, and even widespread detachment was frequently apparent. This separation can also be accentuated by fixatives, especially by alcohol.

The incidence of intralobular hepatic edema in the 45 cases of acute fatal rheumatic fever was as follows: in the first group (14 cases of

41. Rössle, R.: Die Veränderungen der Blutkapillaren der Leber und ihre Bedeutung für die Histogenese der Lebercirrhose, Virchows Arch. f. path. Anat. **188**:484-527, 1907.

42. Keschner, H. W., and Klemperer, P.: Frequency and Significance of Hepatic Edema, Arch. Path. **22**:583-592 (Nov.) 1936.

initial acute fatal rheumatic fever with no previous rheumatic cardiovalvular disease) 11 times; in the second group (10 cases of acute rapidly fatal rheumatic fever with previous chronic rheumatic cardiovalvular disease) 8 times, and in the third group (21 cases of a more prolonged attack of fatal rheumatic fever with previous chronic cardiovalvular disease) 13 times. In 1 case in the last group severe arterial lesions, characterized by enormous intimal proliferation and striking periarterial fibrosis, were present in the liver. In all, intralobular hepatic edema was present in 32 of the 45 cases of acute rheumatic fever, or 71 per cent (79 per cent of the cases of rapidly fatal disease and 62 per cent of the cases of more prolonged disease). Contrast this with the finding of hepatic edema by Keschner and Klemperer in 39 per cent of all cases of cardiac insufficiency, both rheumatic and vascular in origin, and the finding of hyaline membranes in the respiratory bronchioles in 36 per cent of our cases of acute rheumatic fever. In all but 3 of the instances in which the hyaline bands occurred in the lungs intralobular hepatic edema also was present. The presence of intralobular hepatic edema in cases of acute rheumatic fever impresses us as further evidence of the generalized increased permeability of the capillary wall in this disease, and this generalized permeability affords an explanation for the alveolitis consisting mainly of the seroalbuminous extravasation into the alveolar tree and the formation of the hyaline membranes along the walls of the respiratory bronchioles.

## SUMMARY AND CONCLUSIONS

A study has been presented of the observations at autopsy in the lungs in 45 consecutive cases of acute rheumatic fever, selected regardless of the presence or absence of any clinical and gross pathologic pulmonary changes. Such a selection has enabled us to reconstruct the chronologic sequence of events in the development of the pathologic process in the lung from the purely microscopic stage, in which no clinical signs could have occurred, to the stage at which pulmonary damage is clinically manifest.

We were fortunate in having an opportunity to study 14 cases of acute rheumatic fever, fatal in the initial attack, in which chronic cardiovalvular disease with chronic stasis in the lungs was absent. In some instances the entire course of illness lasted only a few days, which enabled us to observe the earliest changes possible in the lungs during acute rheumatic fever. In addition, 31 cases of acute rheumatic fever were studied in which one or more previous attacks had resulted in antecedent cardiovalvular disease with anatomic valvular changes. Here we had an opportunity to study the combination of the effects of previous pulmonary stasis secondary to chronic valvular disease and the immediate effects of the acute and fatal attack.

From the examination of these 45 cases of acute fatal rheumatic fever we believe that the pulmonary changes can be chronologically tabulated thus:

The first stage consists of passage of considerable fluid into the alveoli, septums and interlobular spaces, with marked congestion of alveolar capillaries, engorgement and diapedesis of erythrocytes, together with desquamation of large mononuclear cells into the alveoli. This alveolitis is nonfibrinous and nonbacterial and strongly suggests alterations in the capillaries, with resultant increased permeability and diapedesis of erythrocytes and transudation of albuminous fluid into the alveoli. Hyaline membranes are formed in the respiratory bronchioles and the alveolar ducts in about 50 per cent of the cases.

As the disease is prolonged this stage is followed by thickening and infiltration of the interlobular septums with mononuclear cells, with resultant fibrosis and organization. The smaller arteries show occasional thickening. Gross examination of the lungs at this stage reveals many patchy foci of dark red, fleshy, noncrepitant, nonaerated areas, which have a peculiar india rubber consistency. This stage has been observed in the 14 cases in which death was due to the initial attack of rheumatic fever and in which no previous valvular disease had existed.

In all the remaining cases evidence of previous cardiovalvular disease with resultant pulmonary congestion was found, with the familiar effects of more or less long-standing stasis. But in many cases, in addition to the chronic stasis engendered by the previous attacks, we also observed the evolution of an acute stage similar to that described for the cases of fatal initial attack. And in 9 cases typical hyaline membranes were seen. No Aschoff bodies were found in the lungs in any of the 45 cases.

Twenty cases of chronic rheumatic cardiovalvular disease, mitral stenosis, in which the patient died of intercurrent disease or of chronic heart failure without evidences of rheumatic fever; 23 cases of coronary arterial disease in which the patient died of heart failure, and 16 cases of hypertensive heart disease, with failure, were similarly studied to consider the possibility that the pulmonary lesions seen in cases of acute rheumatic fever were a result of the pulmonary stasis of congestive heart disease. In none of the control cases was a picture observed which approached in similarity that seen in cases of acute fatal rheumatic fever.

The mechanism of the formation of the hyaline membranes in the lungs is dependent on the following factors (and not on any specific infection, such as rheumatic fever or influenza, as had been previously believed): (1) material capable of taking the characteristic eosin stain; (2) air in the alveolar spaces, probably under greater than normal

tension; (3) partial obstruction to the passage of the air by semifluid material in the air passages, and (4) dyspnea, which may be interpreted as violent inspiratory efforts to force air by this obstruction.

The alveolitis and the formation of hyaline membranes are in our opinion a result of an alteration in vascular permeability, with resultant diapedesis of erythrocytes and transudation of seroalbuminous fluid from the capillaries into the alveoli. This vascular damage has been found in cases of rheumatic fever in various other organs of the body. We have seen involvement of the main pulmonary artery and also, in several instances, severe inflammatory arteritis of the various branches of the pulmonary artery in the lungs in the cases presented.

As further evidence of the tendency to vascular damage in rheumatic fever, resulting in increased permeability of the capillary wall, we have found intralobular hepatic edema in 71 per cent of the 45 cases of acute fatal rheumatic fever.

In conclusion, we believe that:

1. A specific rheumatic lung or rheumatic pneumonia cannot be considered to exist. Aschoff bodies were not found in a single instance.

2. A characteristic, though not specific, pulmonary picture is present, which consists of alveolitis, marked congestion, edema, engorgement and the formation of hyaline membranes.

3. These lesions are considered to be a result of damage to the capillaries, with resultant alterations in vascular permeability.

4. Vascular damage was likewise present in the main pulmonary artery and its branches and in the hepatic capillaries.

5. This vascular change corresponds to the involvement seen in the arterial tree in various organs of the body in acute rheumatic fever.

# TUBERCULOMA OF HYPOPHYSIS WITH INSUFFICIENCY OF ANTERIOR LOBE

## A CLINICAL AND PATHOLOGIC STUDY OF TWO CASES

JACK D. KIRSHBAUM, M.D.
AND
HERMAN A. LEVY, M.D.
Instructor in Medicine, University of Illinois College of Medicine
CHICAGO

As early as 1844 von Rokitansky [1] noted the rarity of tubercles in the hypophysis. Both Anderson [2] and Scott and Graves [3] (in a review of the literature to 1933) found no recorded cases of tuberculoma of the hypophysis in the literature. Certain authors [4] failed to mention the existence of tuberculous involvement of this endocrine gland, while others [5] concurred in the opinion that it was rare. Garland and Armitage,[6] in examining 3,533 brains post mortem, found that only *2* of 89 intracranial tuberculomas involved the sella turcica. Falta [7] mentioned that von Frankl-Hochwart found *7* instances of a tubercle in *97* cases of tumor

---

From the Department of Pathology (Woodlawn Hospital), Cook County Hospital, and the Division of Surgery, Northwestern University (Dr. Kirshbaum).

1. von Rokitansky, C.: Handbuch der speziellen pathologischen Anatomie, Vienna, Braumüller & Seidel, 1844, vol. 1; cited by Kraus.[10]

2. Anderson, F. N.: Tuberculoma of the Central Nervous System, Arch. Neurol. & Psychiat. **20**:354 (Aug.) 1928.

3. Scott, E., and Graves, G. O.: Tuberculomas of the Brain, Am. Rev. Tuberc. **27**:171 (Feb.) 1933.

4. Courville, C. B.: Pathology of the Central Nervous System, Mountain View, Calif., Pacific Press Publishing Association, 1937. Frazier, C. H.: Review, Clinical and Pathological, of Parahypophyseal Lesions, Surg., Gynec. & Obst. **62**:1 (Jan.); 158 (Feb.) 1936.

5. Davidoff, L. M.: Diagnosis of Tumors in and Around the Pituitary Gland, New York State J. Med. **36**:1610 (Nov. 1) 1936. Van Wagenen, W. P.: Tuberculoma of the Brain, Arch. Neurol. & Psychiat. **17**:57 (Jan.) 1927. Schidlowsky, P.: Zur Frage der Tuberkulome des zentralen Nervensystems, Arch. f. klin. Chir. **155**:703, 1929. Bucy, P. C.: The Hypophysis Cerebri, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2.

6. Garland, H. G., and Armitage, G.: Intracranial Tuberculoma, J. Path. & Bact. **37**:461 (Nov.) 1933.

7. Falta, W.: Endocrine Disease, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1923.

of the hypophysis without acromegaly. Houssay [8] stated that "circumscribed tuberculous lesions affecting the pituitary as well as metastatic lesions from distant foci and invasion from neighboring tissues have been described," and listed twenty-one references to the literature. Simonds [9] was able to collect records of 28 instances of tuberculous invasion of the pituitary gland, in 10 of which the disease was miliary, while in the rest the tubercles were conglomerate. A similar review was later published by Kraus.[10] Riecker and Curtis,[11] in a review of the autopsies in 24 cases of Simmonds' disease, reported tuberculosis as the destructive agent in 2 instances. Kurzak [12] found 32 cases of tuberculous disease of the hypophysis. More recently Berblinger [13] described the necropsy observations in the case of a 52 year old woman with hypophysial tuberculosis, with an excellent review of the subject. We have encountered 2 cases of tuberculosis of the anterior lobe producing symptoms of pituitary insufficiency among 14,160 autopsies performed by members of the department of pathology of the Cook County Hospital from 1929 to 1940 inclusive. Among these there were 652 cases of various types of pulmonary tuberculosis and 368 cases of tuberculous meningitis; in none of the latter was there hypophysial involvement.

## REPORT OF CASES

CASE 1.—S. J., a white woman aged 37, gave a history of amenorrhea, marked asthenia, severe headaches accompanied by nausea and vomiting and a loss of 50 pounds (22.7 Kg.) of weight in seven months. She had been treated with some form of glandular material by injection for the absence of menstruation, with no effect. She had one living child, of a normal pregnancy and an uneventful puerperium; she had had no miscarriages. There was nothing of significance in her past or family history.

Examination revealed she was undernourished and apathetic, with a blood pressure, expressed in millimeters of mercury, of 70 systolic and 50 diastolic. She weighed 109 pounds (49.4 Kg.). Her skin and hair were dry, and the former was scaly; the eyegrounds showed blurring of the margin of the right disk, and

8. Houssay, B. A.: Hypophysis and Resistance to Intoxications, Infections and Tumors, New England J. Med. **214**:1128 (June 4) 1936.

9. Simonds, J. P.: Tuberculosis of the Hypophysis, in Barker, L. F., and others: Endocrinology and Metabolism, New York, D. Appleton and Company, 1922, vol. 1.

10. Kraus, E. J.: Die Hypophyse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

11. Riecker, H. H., and Curtis, A. C.: Hypophyseal Cachexia (Simmonds' Disease), J. A. M. A. **99**:110 (July 9) 1932.

12. Kurzak, H.: Die Tuberkulose des Keilbeins und ihre Beziehungen zur Hypophyse, Ztschr. f. Tuberk. **34**:433, 1921.

13. Berblinger, W.: Hypophysentuberkulose als Todesursache, Schweiz. med. Wchnschr. **69**:1217 (Dec. 2) 1939.

the left fundus was normal. The fields of vision were not determined. The breasts were flat and atrophic. No other abnormalities were noted.

Laboratory studies gave the following results: urine, normal; hemoglobin concentration, 89 per cent (Sahli); red cell count, 5,720,000 per cubic millimeter; white cell count, 11,400 per cubic millimeter, with 53 per cent neutrophils, 2 per cent eosinophils, 2 per cent basophils, 39 per cent lymphocytes and 4 per cent monocytes. The Wassermann and Kahn reactions of the blood were negative. The basal metabolic rate varied from —21 to —29 per cent. Chemical studies of the blood yielded information as follows (values are expressed in milligrams per hundred cubic centimeters of serum or plasma): calcium, 9.21; phosphorus,

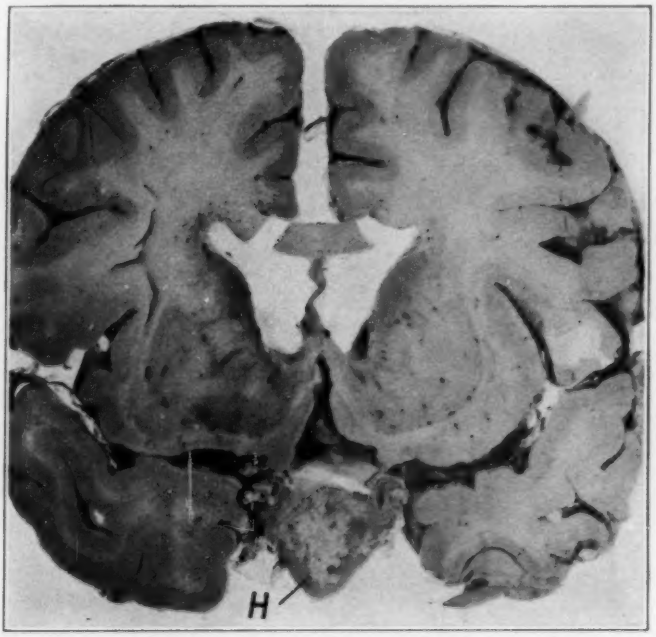



Fig. 1 (case 1).—The hypophysis (*H*) is attached to the brain. Note the marked enlargement of the anterior lobe and its similarity to a tumor.

4.00; nonprotein nitrogen, 44.00; uric acid, 5.5, and sodium, 345.00 (normal 330.00). An oral dextrose tolerance test showed a fasting value of 79 mg. per hundred cubic centimeters, and after ingestion of 100 Gm. of dextrose the values at one hour intervals were 115, 93 and 70 mg. per hundred cubic centimeters of venous blood. Roentgenologic studies showed increased hilar markings in the lungs, thickening of the right apical pleura and a sella turcica of normal size, with no erosion of the clinoid processes of the sphenoid bone.

The diagnosis was insufficiency of the anterior lobe of the pituitary of undetermined origin. Treatment during the diagnostic period consisted of a high vitamin, high calory diet, on which the patient gained 10 pounds (4.5 Kg.).

Before more specific therapy was started, the patient suddenly fainted and died, after a short period of Cheyne-Stokes respiration.

*Necropsy* (performed by J. D. K.).—The right pleural cavity was partially obliterated by dense fibrous adhesions. An area of healed fibroindurative tuberculosis was present in the apex of the right lung. The thyroid gland was small and weighed 8.5 Gm. The two adrenal glands weighed 18 Gm. The uterus measured 7 by 5.5 by 2.5 cm.; its wall was firm and 16 mm. thick. The endometrium was smooth and contained a single flat polyp, 5 mm. in length, and a firm subserous nodule, 2 mm. in diameter. The oviducts were thin walled and

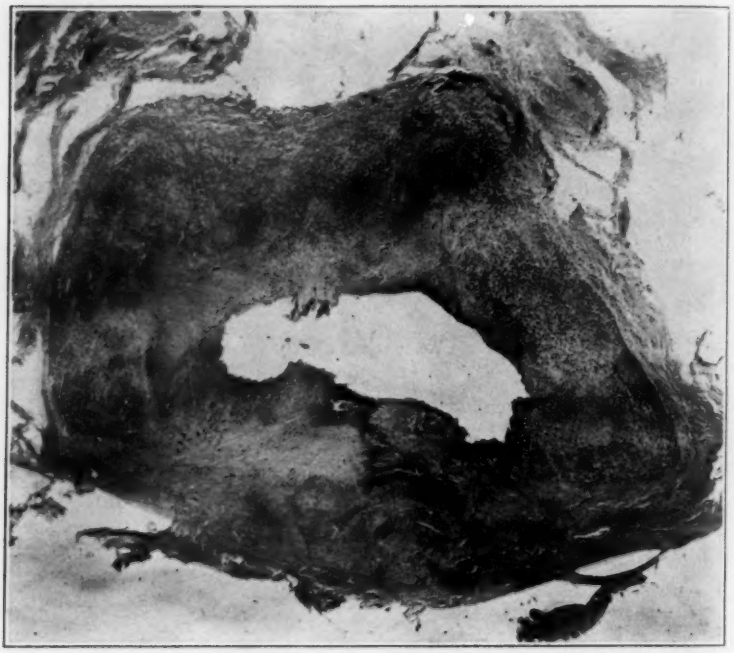


Fig. 2 (case 1).—The anterior lobe of the hyphophysis (low magnification). Note the central area of caseation necrosis.

patent. Each ovary measured 35 by 18 by 10 mm., and the left one contained a single follicular cyst, 12 mm. in diameter. The anterior lobe of the hypophysis was transformed into a tumor mass measuring 30 mm. in transverse diameter, 17 mm. in anteroposterior diameter and 12 mm. in vertical diameter (fig. 1).

The optic nerves were slightly compressed. The cut surface of the tumor appeared light grayish white, mottled with single and confluent light yellow areas, which occupied about two thirds of the surface of the section.

*Microscopic Examination.*—The tumor was a tuberculoma, replacing most of the anterior lobe of the hypophysis and leaving only a narrow rim of intact acini in the periphery (fig. 2). The central portion of the tuberculoma showed areas of caseation necrosis, which in turn were surrounded by a zone of fibrillar and

hyaline connective tissue, often interrupted by groups of plasma cells, eosinophils, leukocytes, lymphocytes and large mononuclear cells. Scattered about were single typical Langhans giant cells and nests of epithelioid cells (fig. 3). The intact peripheral zone of hypophysial tissue showed a preponderance of eosinophilic cells (fig. 4). The capsule was extremely thickened and showed marked fibrosis, with foci of plasma cells, lymphocytes and polymorphonuclear leukocytes. The stalk showed similar infiltrations with single giant cells. The posterior lobe was

Fig. 3 (case 1).—A photomicrograph of the periphery of the tuberculoma taken under high magnification, showing several giant cells of Langhans and extensive fibrosis.

intact and normal. No tubercle bacilli were seen in sections stained after the Ziehl-Neelsen method.

*Anatomic Diagnosis.*—The diagnosis made at autopsy was caseous tuberculosis (tuberculoma) of the anterior lobe of the pituitary gland with extension into the stalk, hypoplasia of the thyroid gland, healed fibroindurative tuberculosis of the apex of the upper lobe of the right lung, fibrous obliteration of the pleural cavity, marked edema of the brain, fatty degeneration of the liver, parenchymatous degeneration of the myocardium and the kidneys, endometrial polyp and pronounced emaciation.

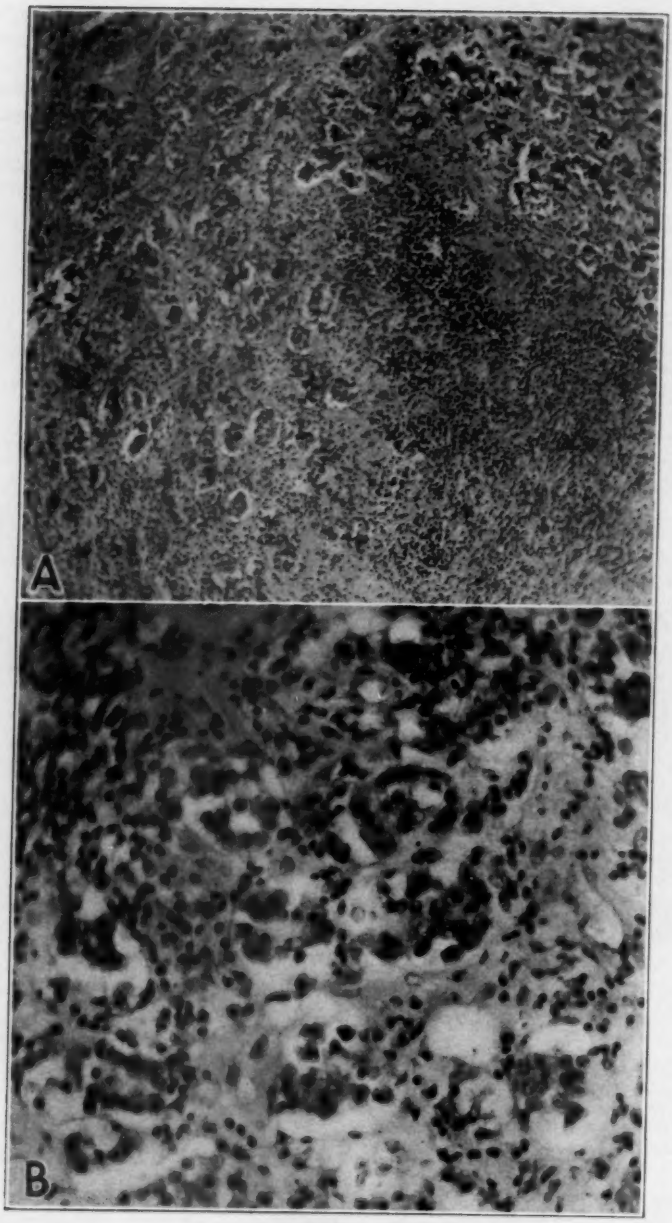



Figure 4

*(See legend on opposite page)*

CASE 2.—P. M. was a white man aged 44. According to a history obtained from his sister, his vision and hearing had begun to fail thirty years before his admission to the hospital. Gradually the loss increased, so that for the past eight years he had been totally blind and deaf. For three years he had suffered from severe dizzy spells, with increasing difficulty in walking, and for two years he had been completely bedridden. Except for pneumonia in childhood, he had had no significant past illness.

On examination he did not appear acutely ill. His skin was smooth, dry and yellowish, and his hair was dry and tough. His blood pressure, measured in millimeters of mercury, was 80 systolic and 60 diastolic. He showed practically no response to either light or sound. Examination of the eyes revealed clouding of the lens and scleral irregularities. The hair of the face and pubic region was thin and scanty. The penis was small, and the right testis was undescended. Also the musculature was generally flaccid, and the anterior and posterior cervical lymph nodes were involved on both sides. Blood counts showed 4,450,000 red corpuscles and 9,600 white corpuscles per cubic millimeter, with 51 per cent neutrophils, 42 per cent lymphocytes and 7 per cent eosinophils. The hemoglobin concentration (Sahli) was 81 per cent. Analysis of the gastric contents showed nothing abnormal. No albumin or sugar was found in the urine. A dextrose tolerance test showed a fasting blood sugar value of 60 mg. per hundred cubic centimeters, and after 100 Gm. of dextrose was administered orally, the blood sugar values, determined at hourly intervals, were 107, 120, 140 and 148 mg. per hundred cubic centimeters of venous blood. The Kahn and Wassermann reactions both of blood and of spinal fluid were negative. Roentgen examination of the chest and the sella turcica showed no abnormality. The patient could not cooperate for determination of the basal metabolic rate. No definite etiologic diagnosis was made, although hypopituitarism was considered as one of the possibilities. The patient vegetated in the hospital for several months and died from what was thought to be terminal bronchopneumonia.

*Necropsy* (performed by Dr. R. H. Jaffé).—The two adrenal glands weighed 11 Gm. and had narrow cortices. The thyroid weighed 10 Gm. and appeared light purple-gray and uniformly granular. The hypophysis measured 9 by 8 by 6 mm. and was soft in consistency. Permission to remove the eyes for examination was not given.

*Microscopic Examination.*—The adrenal cortex was narrow and consisted mainly of zona glomerulosa and pigmented zona reticularis. Of the zona fasciculata there was left only an occasional adenoma-like rest, composed of polygonal cells with ample, finely granular cytoplasm. The adrenal medulla was well preserved. The thyroid gland consisted of medium-sized, colloid-filled follicles with a flat epithelial lining; there were many interstitial lymph nodules centered about congested capillaries. The seminiferous tubules of the testes were largely atrophic and were separated by an increased amount of stroma; the basement membrane was thickened. In a few single tubules there were active proliferation and for-

---

EXPLANATION OF FIGURE 4

Photomicrographs under high magnification of areas in the periphery of the tuberculoma (case 1), from the section shown in figure 2. Note (*A*) the extensive replacement of the acinar structure by tuberculous granulation tissue and (*B*) the remnants of widely separated acini in the periphery of the anterior lobe.

mation of mature spermatozoa. No definite interstitial cells were identified. The posterior lobe of the hypophysis was intact. The anterior lobe was completely replaced by dense connective tissue with scanty, deeply stained nuclei. In places the connective tissue was infiltrated with small round cells of lymphocytic type and single larger histiocytes. Here and there giant cells of Langhans type with peripheral oval nuclei were noted, as well as an occasional small group of epithelioid cells with ample cytoplasm. No tubercle bacilli were found in sections stained by the Ziehl-Neelsen method. In methylene blue–stained sections were a few cuboidal cells with frayed borders and oval nuclei, the cytoplasm of which contained vacuoles and coarse, deep blue granules.

The cuboidal cells were distinctly different from the mast cells, which had a purple-red, metachromatic granulation. Blood vessels of capillary type were scanty; in sections stained for elastic tissue the sclerosed areas were found to be devoid of elastic fibrils. The small arteries and veins near the sclerosed areas were unchanged. Although sections were taken at many different levels, no intact parenchyma could be detected. Sections of the brain from the subthalamic region, the infundibulum, the optic chiasm and the lentiform nucleus revealed nothing abnormal except slight thickening of the walls of smaller arteries and congestion of the capillaries.

*Anatomic Diagnosis.*—The diagnosis made at necropsy included sclerosed tuberculoma of the anterior lobe of the pituitary gland, female distribution of body hair, atrophy of the adrenal cortex and fibrocaseous tuberculous primary complex in the lower lobe of the right lung.

## COMMENT

Our first case fulfils the criteria of pituitary cachexia (Simmonds' disease), with the clinical syndrome of amenorrhea, severe asthenia, marked and rapid loss of weight with cachexia, hypotension, dryness of the skin and hair, low basal metabolic rate and high dextrose tolerance. The picture is completed by the pathologic findings of complete destruction of the anterior lobe of the hypophysis by a tuberculous lesion, with evidence of chronic pulmonary tuberculosis and hypoplasia of the thyroid. The absence of adrenal cortical atrophy is consistent with a diagnosis of Simmonds' disease, according to Silver.[14]

In our second case, although such clinical symptoms of pituitary failure as eunuchoid body build with female distribution of hair and hypotension were present, we observed an old sclerosed tuberculoma of the anterior lobe, with atrophy of the zona fasiculata of the adrenal cortex and possibly the results of pressure on the seventh cranial nerve and the optic chiasm.

Although hypofunction of the pituitary gland was suspected clinically, particularly in the first case, and rediagnosed, tuberculosis as the etiologic factor was not suspected in either case, because of its rarity.

14. Silver, S.: Simmonds' Disease (Cachexia Hypophyseopriva), Arch. Int. Med. **51**:175 (Feb.) 1933.

As described by Simonds [9] and Berblinger,[13] the pathologic picture of tuberculosis of the hypophysis may be associated with, or secondary to, the following conditions: (1) an acute miliary spread of the disease, (2) nearby meningitis or osteomyelitis of the sphenoid bones or (3) a hematogenous metastasis, with formation of large but slow-growing conglomerate tubercles. The first two forms, which are acute, run a rapid course and usually terminate in early death; they do not progress to produce local symptoms, or if symptoms are present they are overshadowed by the general picture of the causative syndrome. The third form, however, can produce various syndromes as a result of pressure on the pituitary gland and on surrounding important structures, as would any other lesion in the same area. Both cases are probably examples of early miliary generalized tuberculosis (according to Ranke's classification), with latent exacerbation in the hypophysis and no activity in the lungs.

Simonds [9] stated, "Tuberculosis of the hypophysis is only rarely associated with symptoms referable to that gland, although in many of the recorded cases, clinical data are very imperfectly reported." However, depending on the exact site of the lesion, its size, rate and direction of growth and the age at which the patient is affected, many varied syndromes (according to Berblinger [13]) can be produced.

The lesion may result in the manifestations of any nonspecific expanding lesion in this area of the brain, such as paralysis of the abducens or the oculomotor nerve, bitemporal hemianopia or amaurosis resulting from compression of the seventh nerve. Thus, blindness occurred in cases reported by Boyce and Beadles [15] and by Beck,[16] as well as in our second case. Recently Coleman and Meredith [17] described a case of diffuse tuberculosis of the pituitary gland, associated with enlargement of the sella turcica, primary atrophy of the optic nerve and bitemporal hemianopia, in which the growth simulated a tumor. They were able to remove the mass surgically, with complete recovery from the visual defects and no evidence of recurrence at the end of three and a half years.

Also the clinical syndrome of adiposogenital dystrophy (Fröhlich's) can be produced from involvement of the diencephalon or the hypothalamus, as described by Kraus.[18]

---

15. Boyce, R., and Beadles, C. F.: A Further Contribution to the Study of the Pathology of the Hypophysis Cerebri, J. Path. & Bact. **1**:359, 1892.

16. Beck: Tuberkulöse Entartung des Hirnanhanges als Ursache der Diplopie und des Strabismus, Ztschr. f. Ophth. **4**:401, 1835; cited by Heidkamp, H.: Beitrag zu Tuberkulose der Hypophyse, Virchows Arch. f. path. Anat. **210**:445, 1912.

17. Coleman, C. C., and Meredith, J. M.: Diffuse Tuberculosis of the Pituitary Gland Simulating Tumor with Postoperative Recovery, Arch. Neurol. & Psychiat. **44**:1076 (Nov.) 1940.

18. Kraus, E. J.: Zur Pathogenese der Dystrophia adiposogenitalis, Med. Klin. **20**:1290 (Sept. 14) 1924.

If the neurohypophysis is attacked diabetes insipidus or polyuria may result, as noted in 4 of Simonds'[9] cases.

Pituitary cachexia, or Simmonds' disease, due to a destructive lesion of the glandular parenchyma of the anterior lobe, is only rarely caused by tuberculosis. Simmonds[19] expressed the opinion that tuberculosis was an infrequent cause of the syndrome named after him. Silver,[14] in a review of 42 cases of Simmonds' disease in which the diagnosis was confirmed by necropsy, mentioned the report of Schlagenhafer[20] and that of Budde[21]; in the latter multiple areas of necrosis, resulting either from tuberculosis or syphilis, were described. Our first case and those reported by Schlagenhafer[20] and Berblinger,[13] and possibly those reported by Froboese,[22] Knoll[23] and Schneider[24] (no autopsy), are examples of Simmonds' disease caused by tuberculosis of the pituitary gland.

## SUMMARY

Two cases of tuberculoma of the hypophysis with autopsy are reported, 1 with the clinical picture of pituitary cachexia and the other with associated eunuchoidism, blindness and deafness.

Tuberculosis of the hypophysis is rare.

The hypophysis may be involved in one of three ways: (*a*) acute miliary spread of the disease, (*b*) extension from contiguous basilar meningitis or sphenoid osteomyelitis or (*c*) hematogenous dissemination with latent exacerbation producing conglomerate tubercles.

Symptoms referable to the hypophysis are not usually associated with the first two types, while in the hematogenous form the symptoms depend on the part of the gland and the surrounding structures involved.

Pituitary cachexia (Simmonds' disease) is rarely due to the destructive effect of tuberculosis, since there are reports of probably only 3 authentic cases, including ours, and 3 more doubtful ones.

---

19. Simmonds, M.: Ueber Tuberkulose der Hypophysis, Zentralbl. f. allg. Path. u. path. Anat. **25**:194 (Feb.) 1914.

20. Schlagenhafer: Zur Kachexie hypophysären Ursprungs, Virchows Arch. f. path. Anat. **222**:249, 1916.

21. Budde, M.: Zur Kenntnis der bösartigen Hypophysengeschwülste und hypophysären Kachexie, Frankfurt. Ztschr. f. Path. **25**:16, 1921.

22. Froboese, C.: Die tuberkuloses Erkrankung der Hypophysis, insbesondere über die primäre Form, Zentralbl. f. allg. Path. u. path. Anat. **29**:145 (March) 1918.

23. Knoll, W.: Beitrag zum Bilde der hypophysären Kachexie, Wien. Arch. f. inn. Med. **4**:555, 1922.

24. Schneider, H.: Kachexie bei wahrscheinlich fort geleiterer Hypophysentuberkulose, Wien. med. Wchnschr. **72**:233 (Jan. 28) 1922.

# METABOLISM IN ORGANIC HYPERINSULINISM

## II. EFFECTS OF EPINEPHRINE ON GLYCEMIC LEVEL AND ON COMBUSTION OF CARBOHYDRATE

JEROME W. CONN, M.D.
AND
ELIZABETH STERN CONN, M.D.
ANN ARBOR, MICH.

The effects of the administration of epinephrine on the metabolism of carbohydrate in normal human subjects and in normal animals have been studied extensively.[1] With regard to the specific effect of epinephrine on total combustion of carbohydrate in the normal organism there is great disagreement. Colwell and Bright,[1f] using normal intact animals, showed that the slow, continuous infusion of a solution of

From the Department of Internal Medicine, University of Michigan Medical School.

The expense of these studies was defrayed in part by a grant from the Horace H. Rackham and Mary A. Rackham Foundation.

1. (*a*) Cori, C. F., and Cori, G. T.: Mechanism of Epinephrine Action: Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, J. Biol. Chem. **79**:309, 1928; (*b*) Mechanism of Epinephrine Action: Influence of Epinephrine and Insulin on Carbohydrate Metabolism of Rats in Postabsorptive State, ibid. **79**:321, 1928; (*c*) Mechanism of Epinephrine Action: Influence of Epinephrine on Utilization of Absorbed Glucose, ibid. **79**:343, 1928; (*d*) Mechanism of Epinephrine Action: Influence of Epinephrine on Lactic Acid Production and Blood Sugar Utilization, ibid. **84**:683, 1929. (*e*) Cori, C. F.; Fisher, R. E., and Cori, G. T.: Effect of Epinephrine on Arterial and Venous Plasma Sugar and Blood Flow in Dogs and Cats, Am. J. Physiol. **114**:53, 1935. (*f*) Colwell, A. R., and Bright, E. M.: Use of Constant Glucose Injections for Study of Induced Variations in Carbohydrate Metabolism: Suppression of Glucose Combustion by Continuous Prolonged Epinephrine Administration, ibid. **92**:555, 1930. (*g*) Bridge, E. M., and Noltie, H. R.: Action of Adrenalin on Respiratory Quotient, J. Physiol. **85**:334, 1935. (*h*) Soskin, S.; Priest, W. S., and Schutz, W. J.: Influence of Epinephrine upon Exchange of Sugar Between Blood and Muscle, Am. J. Physiol. **108**:107, 1934. (*i*) Soskin, S.; Essex, H. E.; Herrick, J. F., and Mann, F. C.: Comparative Influence of Epinephrine and of Dextrose on Utilization of Sugar by Muscles, Determined with the Aid of Thermostromuhr Measurements of Blood Flow, ibid. **118**:328, 1937. (*j*) Himsworth, H. P., and Scott, D. B. M.: Action of Adrenalin in Accelerating Removal of Blood Sugar by Peripheral Tissues, J. Physiol. **93**:159, 1938. (*k*) Conn, J. W.; Conn, E. S., and Johnston, M. W.: Effects of Alimentary and Adrenalin Hyperglycemia upon Total Oxidation of Glucose in Normal Humans, J. Nutrition **19** (supp.):16, 1940.

epinephrine hydrochloride resulted in complete suppression of carbohydrate combustion, as indicated by the respiratory gaseous exchange, despite the fact that a continuous, excessive supply of dextrose was being simultaneously infused. They found further that when the nonprotein respiratory quotient reached the level interpreted as indicating exclusive combustion of fat, the recovery of urinary dextrose equaled the intravenous supply and that the cessation of infusion of a solution of epinephrine hydrochloride resulted in diminishing glycosuria, a rising respiratory quotient, diminishing urinary excretion of nitrogen and deposition of glycogen in the liver and in muscle. Cori and his co-workers [2] elaborated these experiments and arrived at similar conclusions. Soskin and his associates,[3] denying the validity of the respiratory quotient as an index of carbohydrate combustion, used other methods for gathering their data. Careful measurements of blood flow through the muscles and of simultaneous arteriovenous differences in blood sugar indicated normal utilization of carbohydrate by the tissues during continuous administration of epinephrine hydrochloride. Himsworth and Scott [1j] found that when the liver was suddenly excluded from the circulation the blood sugar level fell more rapidly if epinephrine hydrochloride was administered. This they interpreted as an accelerating effect of epinephrine on the removal of blood sugar by the peripheral tissues. Thus, depending on the method of investigation, results in animals have indicated (1) that epinephrine does not affect the utilization of carbohydrate by the tissues, (2) that it is capable of suppressing completely the oxidation of carbohydrate in the organism and (3) that it actually increases the rate of utilization of carbohydrate by the tissues. Results [1k] previously reported by us with an associate suggested that in normal human subjects a single injection of a solution of epinephrine hydrochloride either had no effect on or caused mild suppression of the rate of combustion of carbohydrate.

Soskin and Levine [4] presented evidence interpreted as indicating a relation between the rate of carbohydrate utilization and the height of the blood sugar level. The data were obtained from determinations of blood sugar, blood lactic acid and muscle glycogen made on eviscerated dogs. With an associate we [1k] reported that a large rise of the blood sugar level produced in normal human subjects by the administration of epinephrine hydrochloride did not increase the combustion of carbohydrate. If anything, epinephrine decreased the rate of combustion of

2. Cori and others (footnotes 1 *b*, *c* and *e*).

3. Soskin, Priest and Schutz.[1h] Soskin, Essex, Herrick and Mann.[1l]

4. Soskin, S., and Levine, R.: Relationship Between Blood Sugar Level and Rate of Sugar Utilization, Affecting Theories of Diabetes, Am. J. Physiol. **120**: 761, 1937.

carbohydrate, despite the plethora of circulating blood sugar. On the other hand, a comparable rise in blood sugar produced by the ingestion of dextrose resulted in a marked increase in the rate of carbohydrate combustion. When dextrose and epinephrine were administered simultaneously, despite a tremendous elevation of the blood sugar the same results were obtained as when dextrose alone was given. We concluded, therefore, that the height per se of the blood sugar level does not control the rate of combustion of carbohydrate in the normal human being.

Studies on organic hyperinsulinism afford an unusual opportunity to clarify some of the points in question. The first point involves the validity of the method of indirect calorimetric determination of the rate of combustion of carbohydrate. We have shown by this method [5] that in a case of organic hyperinsulinism evidence of tremendous overcombustion of carbohydrate can be obtained repeatedly, that the spontaneous hypoglycemia observed is due for the most part to this abnormality of metabolism and that the surgical removal of pancreatic islet cell tumors results in return of the normal rate of carbohydrate combustion, as determined by this method, and in disappearance of the hypoglycemic state. Under the conditions of the experiments described it is difficult to interpret in any other way the respiratory quotients obtained.

The second point on which studies on organic hyperinsulinism shed light is the question of hyperglycemia as the stimulus for increasing the rate of combustion of carbohydrate. Early in the development of dietetic therapy for hyperinsulinism it was suggested that the postprandial rise of the blood sugar, associated with the ingestion of a high carbohydrate meal, stimulated a secondary excessive removal of sugar from the blood and resulted, two to five hours later, in a severe hypoglycemic episode. It became customary, therefore, to use diets low in carbohydrate in an attempt to prevent the postprandial rise of blood sugar, with its subsequent secondary fall. The clinical success resulting from measures designed to minimize postabsorptive hyperglycemia [6] seemed to indicate that patients with this condition were extremely sensitive to such stimulus. We showed [5] that in a case of organic hyperinsulinism tremendous overcombustion of carbohydrate results from the ingestion of a standard dose of carbohydrate under controlled conditions. Thus, organic hyperinsulinism represents, among other things, a condition of

5. Conn, J. W., and Conn, E. S.: Metabolism in Organic Hyperinsulinism: I. Quantitative Studies of the Variations in the Rate of Combustion of Carbohydrate Produced by Alterations in the Diet, Arch. Int. Med. **68**:876 (Nov.) 1941.

6. Waters, W. C., Jr.: Spontaneous Hypoglycemia: The Role of Diet in Etiology and Treatment, South. M. J. **24**:249, 1931. John, H. J.: A Case of Hyperinsulinism Treated with Insulin: Preliminary Report, Endocrinology **17**:583, 1933. Conn, J. W.: The Advantage of a High Protein Diet in the Treatment of Spontaneous Hypoglycemia, J. Clin. Investigation **15**:673, 1936.

marked hypersensitivity to the normal stimulus for increasing the rate of combustion of carbohydrate, whether or not a rise of the blood sugar is the actual stimulus. Since a rise of the blood sugar results also from the administration of epinephrine, we considered it important to study in patients with hyperinsulinism the effect on the combustion of carbohydrate of hyperglycemia produced in this way. We are not aware of any similar metabolic study of this condition. (For a clinical description of the patient studied see our preceding report.[5])

In the third place, the clinical observation that injections of a solution of epinephrine hydrochloride are frequently capable of controlling hypoglycemic attacks in cases of organic hyperinsulinism receives a clear explanation from the results of the present study. They justify a clinical procedure which seems indicated under certain circumstances.

## METHOD

A respiration chamber[8] designed for human subjects, with which data from long periods of continuous indirect calorimetry could be gathered, was used. The technic was the same as that described in the preceding paper.[5] In addition, the subjects were taught to give themselves a subcutaneous injection of a solution of epinephrine hydrochloride at a given signal. The dose and the technic of administration were checked by observation through a sealed window of the chamber. Methods of analysis of blood, urine and gases were identical with those previously described.[5] Constant diets were used in preparation for and during all experiments. Normal subjects under identical conditions were used as controls.

## RESULTS

The table shows the results obtained from four hour periods of continuous indirect calorimetry. The results after the subcutaneous administration of a dose equivalent to 1 mg. of epinephrine hydrochloride are compared with those previously obtained in the postabsorptive state, the conditions of the experiments being otherwise identical. It is seen that this amount of epinephrine exerts no significant effects on the rate of combustion of carbohydrate. If influenced at all, the respiratory quotients are slightly decreased. Yet, as will be seen in figure 1, epinephrine provoked a marked increase of the blood sugar level both in the patient and in the control subjects. It should be recalled that under the same conditions of dietary preparation, the ingestion of 60 Gm. of dextrose resulted in a marked increase in the rate of combustion of carbohydrate by the controls and in an excessive increase by the patient.[5]

7. Footnote deleted by the authors.

8. Newburgh, L. H.; Johnston, M. W.; Wiley, F. H.; Sheldon, J. M., and Murrill, W. A.: A Respiration Chamber for Use with Human Subjects, J. Nutrition **13**:193, 1937.

*Combustion of Carbohydrate, Fat and Protein During Four Hour Test Periods in Respiration Chamber*

| Subject | Preparatory Diet (5 Days), with Maintenance Calories | | Test Dose in Chamber; Epinephrine Hydrochloride, Mg. | Total Respiratory Quotient | Nonprotein Respiratory Quotient | Total Heat Produced, Calories | Heat Produced, Protein Calories | Heat Produced, Nonprotein Calories | Source of Nonprotein Calories, Percentage | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carbohydrate, Gm. | Protein, Gm. | | | | | | | Carbohydrate | Fat | |
| Patient *..... | 100 | 80 | 0 | 0.780 | 0.776 | 253 | 39 | 214 | 24.9 | 75.1 | Before operation |
| Patient *..... | 100 | 80 | 0 | 0.794 | 0.792 | 257 | 41 | 216 | 30.6 | 69.4 | Before operation |
| Control *..... | 100 | 80 | 0 | 0.782 | 0.778 | 328 | 56 | 272 | 25.6 | 74.4 | |
| Control *..... | 100 | 80 | 0 | 0.792 | 0.790 | 336 | 48 | 288 | 29.9 | 70.1 | |
| Control *..... | 100 | 80 | 0 | 0.791 | 0.790 | 335 | 48 | 287 | 29.9 | 70.1 | |
| Patient..... | 100 | 80 | 1 | 0.781 | 0.777 | 279 | 39 | 240 | 25.3 | 74.7 | Before operation |
| Control..... | 100 | 80 | 1 | 0.784 | 0.780 | 367 | 56 | 311 | 26.3 | 73.7 | |
| Control..... | 100 | 80 | 1 | 0.782 | 0.778 | 402 | 64 | 338 | 25.6 | 74.4 | |
| Control..... | 100 | 80 | 1 | 0.771 | 0.760 | 372 | 58 | 320 | 21.4 | 78.6 | |
| Control..... | 100 | 80 | 1 | 0.775 | 0.771 | 385 | 39 | 346 | 23.2 | 76.8 | |

* These data are those shown for experiment 3 in the table of our preceding paper.[5] They are reproduced here for direct comparison with data obtained after the administration of epinephrine hydrochloride.

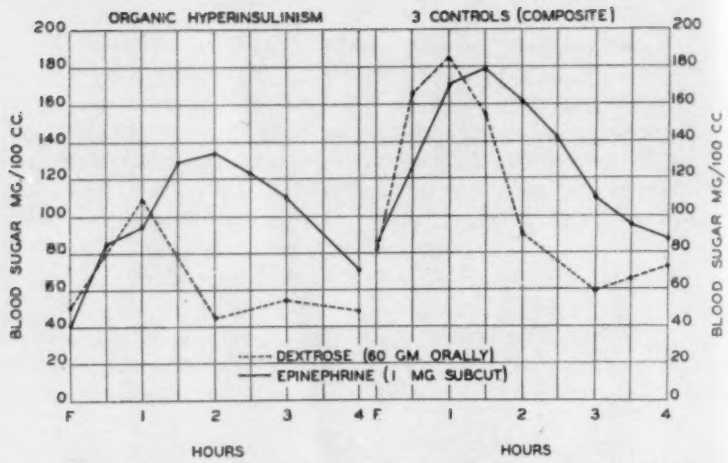



Fig. 1.—Comparison of glycemic responses of a patient with organic hyperinsulinism and of 3 normal subjects after the administration of epinephrine hydrochloride and after the administration of dextrose (preparatory diet: carbohydrate 100 Gm., protein 80 Gm. and maintenance calories).

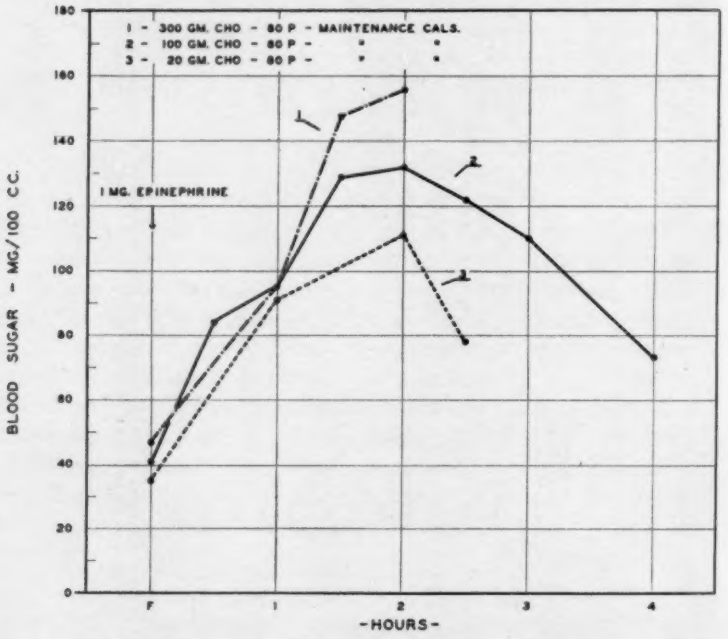



Fig. 2.—Effect of previous diet on glycemic responses to epinephrine hydrochloride.

Figure 1 compares the blood sugar curves of the patient and those of 3 control subjects after (1) the subcutaneous injection of epinephrine hydrochloride and (2) the ingestion of 60 Gm. of dextrose. In all cases the hyperglycemia produced by epinephrine was of the same magnitude as but was more prolonged than that observed after the ingestion of dextrose.

Figure 2 indicates that the glycemic response in the fasting state of a patient in organic hyperinsulinism to 1 mg. of epinephrine hydro-

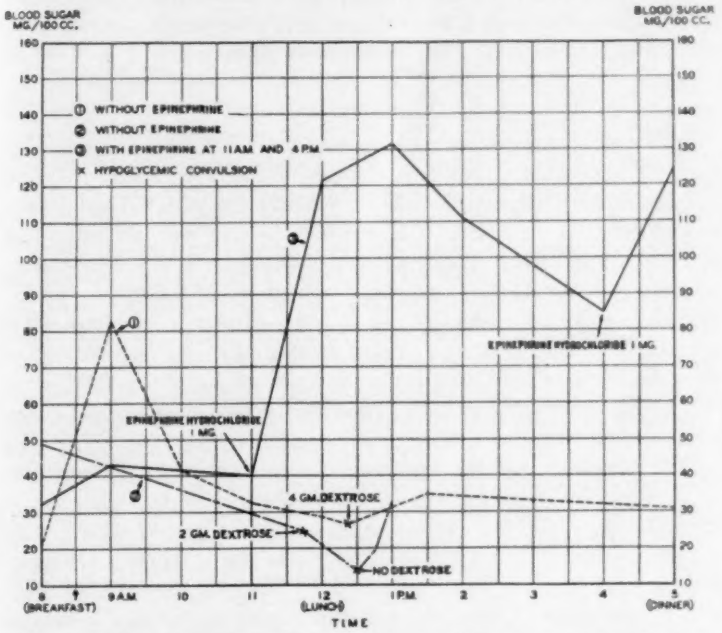



Fig. 3.—Effect of epinephrine hydrochloride on daily sugar curves (diet: carbohydrate 20 Gm., protein 50 Gm. and fat 137 Gm.).

chloride given subcutaneously is related to the carbohydrate content of the antecedent diet.

Results of a third experiment indicated the effectiveness of epinephrine hydrochloride in controlling hypoglycemic convulsions, even under conditions of carbohydrate privation. During an eleven day control period the patient was kept in bed and fed a diet which, although it provided enough calories for maintenance, contained only 20 Gm. of carbohydrate and 50 Gm. of protein for each twenty-four hours. Two to four hypoglycemic convulsions were observed daily. They occurred regularly at two times of day, namely, between 11:30 a. m. and 12:40 p. m. and

between 4:00 and 5:30 p. m. The blood sugar level during attacks ranged from 14 to 34 mg. per hundred cubic centimeters. For the next five days 1 mg. of epinephrine hydrochloride was given subcutaneously at 11:00 a. m. and at 4:00 p. m., the diet remaining the same. No attack occurred during this period. Figure 3 shows the blood sugar level on two successive days during the control period and the effect of epinephrine on the blood sugar level in the second period.

We performed a similar experiment, using 50 mg. of ephedrine sulfate orally six times daily in place of epinephrine hydrochloride. This substitute was only mildly effective. Hypoglycemic convulsions were delayed until from 2:00 to 3:00 p. m. but were not prevented.

## COMMENT

The results indicate that the administration of epinephrine, in amount sufficient to produce a prolonged elevation of the blood sugar level, does not stimulate any increase in the rate of combustion of carbohydrate over that observed in the fasting state, either in persons with organic hyperinsulinism or in normal subjects. Previous observations [1k] and the present ones suggest, on the contrary, that if the rate of oxidation of carbohydrate is at all affected by the amount of epinephrine administered, it is mildly depressed.[9] It can be said, further, that, within the limits of these experiments the height per se of the blood sugar is not related to the rate of combustion of carbodydrate in persons with organic hyperinsulinism or in normal subjects.

We [5] showed that the ingestion of dextrose results in a greatly accelerated rate of combustion of carbohydrate in normal subjects and in an abnormally great increase of the rate in a patient with organic hyperinsulinism. Comparable hyperglycemia (fig. 1) produced, on the one hand, by ingestion of dextrose and, on the other, by the administration of epinephrine hydrochloride produces entirely different effects on the combustion of carbohydrate. Otherwise stated, the addition to the body of extra carbohydrate from outside sources produces an acceleration of the rate of combustion of carbohydrate, while hyperglycemia of endogenous origin does not.

The fact that a rise in the level of the blood sugar induced by epinephrine does not produce a simultaneous increase in the rate of combustion of sugar becomes of practical importance in the medical management of persons with severe organic hyperinsulinism. It is agreed by all

9. Experiments such as these, in which the total respiratory gaseous exchange of a prolonged period is accounted for, eliminate the inaccuracies (produced by temporary shifts in acid-base balance after administration of epinephrine) which have been observed in "short run" collections of respiratory gases.

familiar with the problem that when certain clinical diagnostic criteria [10] have been satisfied, an exploratory operation in search of an islet cell tumor of the pancreas should be done. Unfortunately, tumors are not always found, and the severe hypoglycemia must be treated medically. A diet low in carbohydrate is unsuccessful under these particular circumstances because the liberation of insulin cannot be sufficiently depressed by this means.[5] One is consequently forced to give frequent feedings high in carbohydrate in an attempt to maintain the blood sugar above the "attack level." As was indicated, combustion of carbohydrate is tremendously stimulated under these conditions, and periodic convulsions result. In fact, continuous infusion of dextrose has been necessary in some cases in order to prevent hypoglycemia. The following facts make epinephrine a useful adjunct in the medical management of this condition: 1. The liver in cases of organic hyperinsulinism usually contains large amounts of glycogen.[11] 2. Some of this store of carbohydrate can be mobilized and delivered into the blood by the daily administration of epinephrine without increasing the rate of carbohydrate combustion. These experimental observations were put to clinical test (fig. 3). The use of 1 mg. of epinephrine hydrochloride twice daily was successful in preventing hypoglycemic convulsions on the same dietary plan which had resulted in two to four seizures daily. Wilder,[11a] from his clinical observations, has made the suggestion that the use of epinephrine base in oil might be of benefit in this condition. As already stated, large doses of ephedrine sulfate were ineffective in controlling hypoglycemic attacks.

Finally, discrepancies in the glycemic response after administration of epinephrine hydrochloride in cases of organic hyperinsulinism can be related, at least in part, to differences in the antecedent diet of the patient. If all patients with organic hyperinsulinism were given equal opportunity to accumulate a glycogen reserve by means of a standard preparatory diet,[12] the use of a test dose of epinephrine hydrochloride might bring out significant differences in types and degrees of this disease.

## CONCLUSIONS

1. Epinephrine hydrochloride in sufficient amount to produce prolonged hyperglycemia does not increase the postabsorptive rate of com-

10. Conn, J. W.: The Spontaneous Hypoglycemias: Importance of Etiology in Determining Treatment, J. A. M. A. **115**:1669 (Nov. 16) 1940.

11. (*a*) Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940, p. 376. (*b*) Warren, S.: Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1938, p. 192. (*c*) Conn and Conn.[5]

12. Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, Am. J. M. Sc. **199**:555, 1940.

bustion of carbohydrate, either in persons with organic hyperinsulinism or in normal persons. The respiratory quotient, if at all affected, is slightly depressed.

2. The average height per se of the blood sugar does not control the rate of combustion of carbohydrate. Hyperglycemia of comparable magnitude, produced, on the one hand, by administration of epinephrine hydrochloride and, on the other, by ingestion of dextrose, is associated with wide differences in the rate of oxidation of carbohydrate.

3. In organic hyperinsulinism a rise in blood sugar associated with absorption of dextrose is accompanied by tremendously excessive combustion of carbohydrate. Hyperglycemia produced by epinephrine hydrochloride alone results in no greater oxidation of sugar than that observed in the postabsorptive state.

4. When medical management of patients with severe organic hyperinsulinism becomes necessary, the daily administration of epinephrine hydrochloride is a useful adjunct because (1) the hyperglycemia thus produced is not accompanied by increased combustion of sugar and (2) the excessive inhibition of hepatic glycogenolysis due to hyperinsulinism is partially released.

5. Differences in the glycemic response to epinephrine in cases of organic hyperinsulinism may be due, in part, to the lack of standardized dietary preparation for the test.

# METABOLISM IN ORGANIC HYPERINSULINISM

## III. EFFECTS OF ADRENAL CORTICAL EXTRACT ON BLOOD SUGAR AND ON SODIUM AND NITROGEN EQUILIBRIUM

JEROME W. CONN, M.D.

AND

ELIZABETH STERN CONN, M.D.

ANN ARBOR, MICH.

In 1932 Britton and Silvette [1] demonstrated that the secretion of the adrenal cortex is involved in the metabolism of carbohydrate. The experiments of Long and Lukens in 1936,[2] indicating that severe pancreatic diabetes could be greatly ameliorated by bilateral adrenalectomy, stimulated further investigation of the role of the adrenal cortex in carbohydrate metabolism. Much information has since been obtained with respect to the physiologic processes involved and the specific fractions of the adrenal cortical secretion responsible for the effects produced.[3]

Since 1937 evidence has been presented which indicates that adrenal cortical extracts are capable of raising the blood sugar of normal, starving, starving-hypophysectomized, partially depancreatized and depancreatized-adrenalectomized animals.[4] Further, it has been reported [5] that normal mice are rendered resistant to the hypoglycemic

From the Department of Internal Medicine, University of Michigan Medical School.

The expense of these studies was defrayed in part by a grant from the Horace H. Rackham and Mary A. Rackham Foundation.

1. Britton, S. W., and Silvette, H.: Effects of Cortico-Adrenal Extract on Carbohydrate Metabolism in Normal Animals, Am. J. Physiol. **100**:693, 1932.

2. Long, C. N. H., and Lukens, F. D. W.: Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in Cats, J. Exper. Med. **63**:465, 1936.

3. Long, C. N. H.: Diabetes Mellitus in the Light of Our Present Knowledge of Metabolism, Tr. & Studies Coll. Physicians Philadelphia **7**:21. 1937.

4. (*a*) Corey, E. L., and Britton, S. W.: Hypophyseal and Adrenal Interrelationships and Carbohydrate Metabolism, Am. J. Physiol. **126**:148, 1939. (*b*) Long, C. N. H., and Katzin, B.: Effect of Adrenal Cortical Hormone on Carbohydrate Stores of Fasted Hypophysectomized Rats, Proc. Soc. Exper. Biol. & Med. **38**:516, 1938. (*c*) Corey, E. L.: Hypophyso-Adrenal Synergy and Carbohydrate Metabolism, Am. J. Physiol. **126**:470, 1939. (*d*) Fry, E. G.; Long, C. N. H., and Ritter, H. B.: The Aggravation of Pancreatic Diabetes of Adrenal Cortical Extract, ibid. **126**:497, 1939. Long.[3]

5. Jensen, H., and Grattan, J. F.: The Identity of the Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, Am. J. Physiol. **128**:270, 1940.

effects of insulin by the previous administration of adrenal cortical extracts. These observations, indicating an "anti-insulin" effect of such substances, suggested this investigation. It was felt that cases of organic hyperinsulinism in human beings afforded an opportunity to test the practicability of the laboratory findings.

The subject of this study was a 60 year old woman who was suffering from severe spontaneous hypoglycemia and who, subsequently, was completely cured by the surgical removal of four islet cell adenomas.[6] In order to demonstrate physiologic activity of the adrenal cortical extract used, sodium and nitrogen balance studies were conducted along with the observations on the blood sugar levels.

## METHODS

For the entire period of study the patient was confined to bed, except for the collection of urine and feces, which was facilitated by the use of a commode beside the bed. The carefully weighed diet, which provided enough calories for maintenance, was constant from day to day. The sodium and the nitrogen content of the diet was determined by analysis. The fluid intake was constant. Ten grams of sodium chloride per day, in tablet form, was given with meals.

Determinations of blood sugar were done by the Benedict method.[7] Food and urinary sodium were determined according to the method of Butler and Tuthill,[8] and food, urinary and fecal nitrogen, by the Kjeldahl method.

Adrenal cortical extract[9] was used throughout. The sodium and nitrogen content of the extract was determined and was found to be negligible.

## RESULTS

The results are graphically summarized in figure 1.[10]

*Blood Sugar.*—A diet low in carbohydrate (carbohydrate 20 Gm., protein 50 Gm. and fat 137 Gm.) was used in order to provoke frequent hypoglycemic attacks, the frequency of which could be compared with and without the daily intramuscular injection of 30 cc. of adrenal cortical

6. Conn, J. W., and Conn, E. S.: Metabolism in Organic Hyperinsulinism: I. Quantitative Studies of the Utilization of Carbohydrate Under Various Conditions, J. Clin. Investigation, to be published.

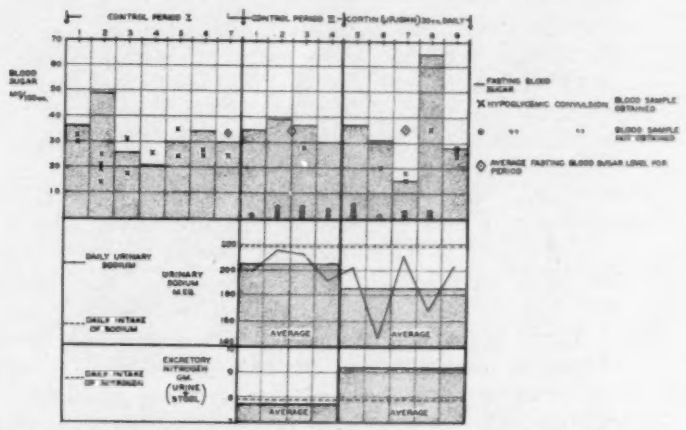
7. Benedict, S. R.: The Analysis of Whole Blood: II. The Determination of Sugar and of Saccharoids (Non-Fermentable Reducing Substances), J. Biol. Chem. **92**:141, 1931.

8. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**: 171, 1931.

9. The extract used (cortin-Upjohn) was supplied by Dr. E. Gifford Upjohn and the Upjohn Co.

10. Control period II was preceded by three days of the control regimen to allow the patient to come into equilibrium with her diet. Determinations were begun on the fourth day. The first day of control period II, therefore, is the fourth day of the control regimen.

extract (5 cc. in each buttock three times daily). The level of fasting blood sugar was determined daily, and the level of the blood sugar during convulsions was obtained in the majority of attacks. Note in the two separate control periods that the average values for the fasting blood sugar were 33 and 35 mg. per hundred cubic centimeters, respectively. During the period of administration of adrenal cortical extract there was somewhat greater variation, both the highest and the lowest values having been obtained then. The average value for the period, however, was 35 mg. per hundred cubic centimeters. Convulsive attacks, occurring between levels of 14 and 35 mg. per hundred cubic centimeters, came one to four times a day, with an average of two times per day in the control periods. When adrenal cortical extract was given they occurred




Effect of adrenal cortical extract on the blood sugar level and on the sodium and nitrogen balance in a case of organic hyperinsulinism (constant diet: carbohydrate 20 Gm., protein 50 Gm., fat 137 Gm. and sodium chloride 10 Gm.).

two to four times daily, averaging three times per day. Thus, the amount and kind of adrenal cortical extract used resulted in no apparent "anti-insulin" or blood sugar–raising effect in this case of organic hyperinsulinism.

*Sodium Balance.*—It may be seen that during the period of administration of the extract there occurred an average daily retention of 22 milliequivalents of sodium, as compared with the quantities excreted during the control period. This represents a retention of 10 per cent of the daily total intake of sodium. It should be noted that wide daily swings of retention and "rebound," above and below the average value, occurred during the period when adrenal cortical extract was given.

This phenomenon has been described by Thorn [11] as occurring in normal human beings receiving large amounts of adrenal cortical extract.

*Nitrogen Balance.*—Nitrogen equilibrium was maintained during the control period. The injection of 30 cc. of adrenal cortical extract daily resulted in an average daily increase of 1.5 Gm. of excretory nitrogen. This amounted to a 20 per cent increase in the excretion of nitrogen over excretion during the control period. The occurrence of a similar increase in nitrogen excretion of rats receiving large doses of adrenal cortical extract has been demonstrated by Long, Katzin and Fry.[12]

## COMMENT

That adrenal cortical extracts are capable of raising the blood sugar level and of increasing the content of glycogen in the liver and muscles of animals kept under a variety of conditions has been indisputably established.[13] It has been shown further that certain fractions of adrenal cortical extracts are much more active than others in these respects.[12] Jensen and Grattan [5] expressed the belief that the so-called glycotropic (anti-insulin) factor of anterior pituitary extracts is identical with the adrenotropic factor and that the anti-insulin effect is produced by virtue of stimulation of the adrenal cortex. They were able to prevent insulin convulsions in mice by previous administration of anterior pituitary extracts containing the adrenotropic fraction, adrenal cortical extracts and corticosterone acetate. Other fractions of anterior pituitary extract (free from the adrenotropic factor) were ineffective.

It must be realized that in all of the aforementioned experiments the amounts of material required to produce these effects in animals have been enormous. It is easily calculated from the experiments of Jensen and Grattan [5] that it required in the mouse 12.5 mg. of crystalline corticosterone acetate (one of the fractions presumably concerned in the metabolism of carbohydrate) to counteract the hypoglycemic effect of 1 unit of insulin [14] and that it required 1,000 dog units of Swingle's adrenal cortical extract to do the same thing. Long,[3] employing the same preparation as that used in this study, gave 48 cc. per kilogram of body weight to produce a substantial rise in blood sugar and liver glycogen and an increased excretion of nitrogen in rats. These amounts are, of

11. Thorn, G. W.: ' Effect of Cortical Hormone on Renal Excretion of Electrolytes in Normal Subjects, Proc. Soc. Exper. Biol. & Med. **36**:361, 1937.

12. Long, C. N. H.; Katzin, B., and Fry, E. G.: Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309, 1940.

13. Britton and Silvette.[1] Long.[3] Footnotes 4 *a*, *b* and *c*.

14. Kuizenga and Cortland (Fractionation Studies on Adrenal Cortex Extract with Notes on the Distribution of Biological Activity Among the Crystalline and Amorphous Fractions, Endocrinology **24**:526, 1939) were able to obtain a yield of only 68 mg. of crystalline corticosterone acetate from 880 Kg. of beef adrenal gland.

course, of an entirely different order of magnitude from what has ever been given a human being, even when allowance is made for differences in metabolic rate and in species. It is not surprising, therefore, that the daily administration to our patient of 30 cc. of adrenal cortical extract (three to four times the amount required to control severe Addison's disease) was incapable of raising the level of blood sugar or of exerting any apparent anti-insulin effect.

On the other hand, a definite physiologic effect on the metabolism of sodium and of nitrogen was observed. This amounted to a daily retention of 10 per cent of the ingested sodium and an excretion of nitrogen which was 20 per cent in excess of the daily intake. The increased catabolism of protein induced by adrenal cortical extract indicates an excessive destruction of body protein, which amounts to about 9.4 Gm. daily. No more than 5 Gm. of dextrose for each twenty-four hour period would be derived in this process. Long [8] expressed the opinion that the source of the extra carbohydrate observed in animals treated with adrenal cortical extracts is found in the increased destruction of protein. Even in the absence of increased utilization of sugar one would hardly expect the addition of 5 Gm. of dextrose poured into the blood evenly over a twenty-four hour period to have any significant effect in raising the blood sugar of an adult human subject.[15] It would appear, therefore, that the rise of blood sugar and glycogen content, demonstrated in laboratory animals, is the result of the use of massive doses of adrenal cortical extracts and their purified derivatives. Physiologic activity of adrenal cortical extracts with regard to sodium and nitrogen metabolism is demonstrable in human beings with much smaller doses.

## CONCLUSIONS

In a proved case of organic hyperinsulinism the daily administration of 30 cc. of adrenal cortical extract exerted no apparent anti-insulin or blood sugar–raising effect.

Simultaneous sodium and nitrogen balance studies indicated the potency of the extract used. There occurred a retention of 10 per cent of the ingested sodium and an excretion of nitrogen which was 20 per cent in excess of the intake.

The amounts of adrenal cortical materials used to produce a rise of the blood sugar in laboratory animals are relatively so large that (1) the results may represent a response which is possible only under distinctly abnormal circumstances and (2) clinical use of the material as an insulin antagonist is impractical with the adrenal cortical extracts now available.

15. Conn, J. W., and Newburgh, L. H.: The Glycemic Response to Isoglucogenic Quantities of Protein and Carbohydrate, J. Clin. Investigation **15**:665, 1936.

# HYPOTHERMIA

## REPORT OF A CASE IN WHICH THE PATIENT DIED DURING THERAPEUTIC REDUCTION OF BODY TEMPERATURE, WITH METABOLIC AND PATHOLOGIC STUDIES

JOHN H. TALBOTT, M.D.

W. V. CONSOLAZIO, B.S.
AND
L. J. PECORA, B.S.
BOSTON

A substantial reduction of body temperature has been employed by several investigators in recent years as a useful therapeutic procedure. It was devised by Smith and Fay [1] originally for the treatment of patients with metastatic malignant growths and has been extended subsequently to the treatment of patients with other conditions.[2] The depression in the internal body temperature which may be produced by the general application of cold to the subject's skin belies common opinion concerning the minimum critical temperature. Internal body temperatures which range from 80 to 90 F. may be maintained continuously, if due precautions are exercised, for as long as seven days. After such a treatment the patient appears to have suffered no undesirable effects. Smith and Fay chose hibernation as a fitting term for the treatment, while others have called it refrigeration, freezing, frozen sleep and crymotherapy. It is believed that a valid criticism may be offered against the selection of any of them. Hypothermia,[2] on the other hand, is exempt from such criticisms and is thought to be a most appropriate term. It will be used to connote a general lowering of the internal temperature of the body to the point where freezing supervenes.

When a new and radical procedure, as in this instance, is introduced into medical therapeusis, as complete data as possible concerning the

---

This study was aided by grants from the Lucius N. Littauer Foundation and the Corn Industries Research Foundation.

From the McLean Hospital, Belmont, Mass.; the Medical Clinic of the Massachusetts General Hospital, and the Fatigue Laboratory, Harvard University.

1. Smith, L. W., and Fay, T.: Observations on Human Beings with Cancer, Maintained at Reduced Temperatures of 75°-90° Fahrenheit, Am. J. Clin. Path. **10**:1, 1940.

2. Talbott, J. H.: The Physiologic and Therapeutic Effects of Hypothermia, New England J. Med. **224**:281, 1941.

direct, as well as the indirect, effects should be collected. The minimum requirements for a comprehensive study might well embrace therapeutic results, physiologic and biochemical variations and morphologic changes. An attempt has been under way recently to fulfil these requirements, and toward this end certain studies of hypothermia either have been reported [3] from our laboratory or are in preparation. This communication presents additional data on the physiologic changes observed during hypothermia, but it is concerned particularly with 1 patient in our series who died during a hypothermic treatment. The patient was a 46 year old man suffering from schizophrenia, who died after two days of continuous hypothermia, while the body temperature was returning to normal.

Reports in the literature of patients who have died after accidental exposure to cold or who have suffered from an advanced stage of a metastatic malignant growth and have died during hypothermia have been inadequate in one respect. In neither circumstance could one be certain that the observed changes were associated with hypothermia per se. On the other hand, the patient under discussion was physically sound before the treatment and was suffering from a mental disorder only. No portion of the body was frozen during treatment, and the observed morphologic changes are believed to be intimately associated with a reduction of body temperature and not complicated by other factors or processes.

The procedure for the induction of hypothermia has been described [4] and will not be repeated in detail. It involves essentially the exposure of an anesthetized nude subject to a cold environment. Cracked ice or blankets especially constructed for the circulation of a refrigerant suffice. In our studies hypothermia was achieved by the latter means. Shortly after exposure to such an environment, the heat-regulatory mechanism is overpowered, and a steady decline in body temperature follows. During hypothermia, the temperature level of the body may be maintained by the regulation of the environmental temperature.

## REPORT OF CASE

W. D., a white, American-born man aged 46, suffered from symptoms of mental disease for more than ten years. He was admitted first to McLean Hospital in 1931. He spent the greater part of the following nine years in that hospital. A diagnosis of schizophrenia was made in 1934. An extremely poor prognosis regarding his mental disease was expressed by several psychiatrists at that time

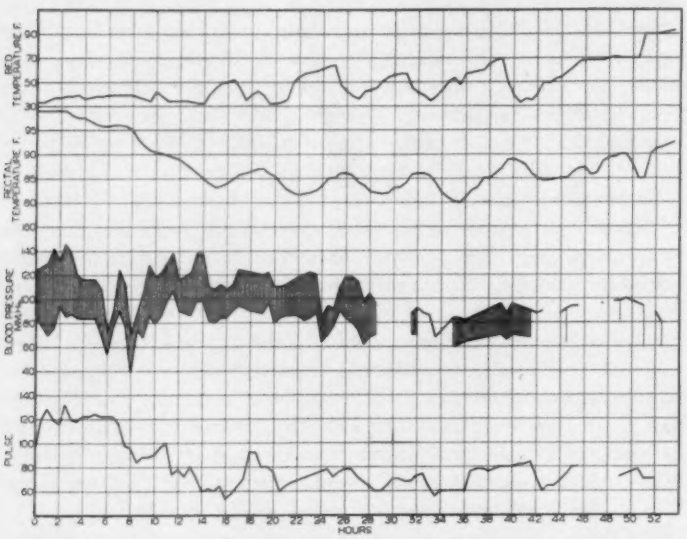
3. (*a*) Talbott, J. H., and Tillotson, K. J.: The Effects of Cold on Mental Disorders: A Study of Ten Patients Suffering from Schizophrenia, Dis. Nerv. Syst. **2**:116, 1941. (*b*) Dill, D. B., and Forbes, W. H.: Respiratory and Metabolic Effects of Hypothermia, Am. J. Physiol. **132**:685, 1941. (*c*) Talbott.[2]

4. Smith and Fay.[1] Talbott.[2]

and was confirmed by others after that. He was given several shock treatments with insulin in 1938. His mental condition became decidedly worse after these.

His physical condition had been satisfactory at all times. A periodic physical examination, as well as the examination which preceded the induction of hypothermia, revealed nothing abnormal. His blood pressure was 124 systolic and 88 diastolic; his body weight was 162 pounds (73.5 Kg.). Frequent routine examinations of the urine and the blood had yielded normal results. Because of these findings, together with the unsatisfactory mental state, it was decided to treat him with a reduction of body temperature.

Hypothermia was instituted on June 19, 1940. Twenty minutes before the induction he was given 0.24 mg. of pentobarbital sodium intramuscularly, followed in eighteen minutes by 0.8 Gm. of evipal sodium (the sodium salt of n-methyl-C-C-




Record of fluctuation in bed temperature and the rectal temperature, blood pressure and pulse rate of a schizophrenic patient during induced hypothermia.

cyclohexylmethyl barbituric acid) administered intravenously. During the first seven hours of hypothermia he was given 1.3 Gm. additional of the last-named drug in divided doses. No other sedative, anesthetic or medicament was administered until he went into circulatory collapse shortly before death two days later.

Eleven hours after induction of hypothermia a nasal gavage tube was inserted. Fifty cubic centimeters of a 5 per cent solution of dextrose in a physiologic solution of sodium chloride was instilled through the tube every hour thereafter. Various investigational procedures were carried out from time to time and were not upsetting to the patient. These included metabolic measurements; electrocardiographic, electroencephalographic and teleroentgenographic examinations of the heart and lungs; drawing of blood for analysis, and determination of circulation time and of renal clearance.

The body temperature reached 83.5 F. sixteen hours after the beginning of the induction. As indicated in the chart, it remained below 98 F. for fifty hours and below 95 F. for forty-five hours before reaching a minimum of 80 F. The initial fall in temperature was slightly slower than the average in our experience, but this patient had a large frame and the room temperature was high. These are adequate reasons for a slow reduction in body temperature.

The clinical response during the first two days under treatment was similar to that observed in other patients, and nothing was noted which gave rise to any undue alarm. During the first three hours of induction the blood pressure and pulse rate were strong and of good quality. A drop in blood pressure followed, but this is the usual response, and it was not considered to be disturbing. Shivering was apparent intermittently throughout the treatment. Below 95 F. there appeared to be no correlation between the severity of shivering and further reduction in body temperature. The duration of the shivering spells was as long when the temperature was below 85 F. as it was at other temperatures.

After the treatment had continued for approximately two days it was decided arbitrarily to terminate it. The flow of refrigerant through the coils in the blankets was stopped. The body temperature rose slowly to 90 F. Nothing had developed up to this time to give rise to serious apprehension for the physical condition of the patient. Owing to a mistake in orders, the patient was taken out of the blankets at this point and allowed to drink water and hot bouillon. A drop of 5 F. in body temperature followed shortly thereafter, which was thought to be incorrect and attributed to a poorly inserted rectal thermocouple. It is believed now that the thermocouple was properly inserted and that the temperature drop as recorded was correct. The blood pressure was 94 systolic and 60 diastolic. The patient was then replaced between the temperature-controlled blankets, and instead of a cold solution circulating through the blankets, as we now know should have been ordered, a solution above body temperature was employed. The body temperature fluctuated rather rapidly, but before the full significance of this was appreciated, the patient was in profound circulatory collapse. The color was cyanotic, the respirations were gasping and shallow and the peripheral pulse was not obtainable. An unsuccessful attempt was made to administer intravenously a solution of dextrose and sodium chloride. Oxygen inhalation and injections of caffeine with sodium benzoate and ephedrine hydrochloride were given terminally, without demonstrable effect. The rectal temperature was 92.5 F. when the patient was pronounced dead, less than one hour after the onset of circulatory shock. This was the maximum it had reached for more than two days. A complete autopsy was performed four hours later.

*Laboratory Studies.*—Routine examinations of the urine were negative for dextrose, albumin and formed elements, but all were positive for acetone and diacetic acid.

Results of roentgenographic examination of the chest were reported by Dr. J. R. Lingley as follows:

"The transverse measurements of the heart shadow and chest taken at 7 feet (2.1 meters) with a fifteen second exposure are:

| Duration of Treatment, Hr. | Heart, Cm. | Chest, Cm. | Rectal Temperature, F. |
|---|---|---|---|
| 0 | 12.7 | 27.1 | 98 |
| 24 | 12.4 | 26.8 | 82 |
| 34 | 11.5 | 27.2 | 82 |
| 48 | 12.2 | 27.5 | 89 |

"Detail in the lung is obscured by motion, and interpretation of the pathologic condition of the lung is impossible."

The concentrations of the constituents of the blood are given in table 1. The methods for analysis of the blood constituents have been described previously.[5]

The electrocardiograms were interpreted by Dr. Ashton Graybiel as follows:

Before hypothermia: "The rhythm is normal, and the rate is 90 beats per minute. The P waves are normal. The PR interval measures 0.18 second. The QRS complexes are slightly slurred, but their duration is 0.08 second, which is within normal limits. The QRS voltage is low but within the normal range. The ST segments are slightly elevated in leads I and II. The T waves are tall and upright in all leads."

After twenty-four hours of hypothermia: "The rhythm is normal, and the rate is 60 beats per minute. The P waves and the PR interval remain unchanged. There has been a slight increase in the amplitude of the R waves. The ST segments are displaced upward to a slightly greater extent in leads I and II than in the control record."

After thirty-four hours of hypothermia: "The rhythm is normal, and the rate is 55 beats per minute. Because of somatic tremor the P waves cannot be delineated with sufficient accuracy to determine the PR interval. The QRS complexes appear to be somewhat longer in duration, but the measurements are not accurate. It is possible that some slight degree of intraventricular block is present. The upward displacement of the ST segments in leads I and II is increased further and is definitely abnormal. The T waves are low in amplitude in leads I and II and are isoelectric in lead III."

After forty-eight hours of hypothermia: "The rhythm is normal, and the rate is 57 beats per minute. The P waves are normal. The PR interval is 0.18 second. The QRS complexes are similar to those in the control record. The ST takeoff is abnormally high in leads I and II. This segment shows considerable concavity in all three leads. The T waves are slightly lower than in the first record."

*Postmortem Examination.*—Because of the interest in this case a complete and extensive autopsy was performed. Only the significant findings will be enumerated. Chemical analyses were made of several different organs and tissues of the body (table 2) in addition to the morphologic studies.

Except for moderate rigor mortis and marked lividity, the exterior aspect of the body was not remarkable.

The brain weighed 1,450 Gm. and was grossly normal. Microscopically there were a few foci of probable degeneration in the cortical nerve cells. A few fresh subependymal hemorrhages were visible in the wall of the third ventricle; there was no cellular reaction. The pituitary was enlarged, measuring 1.9 by 1.2 by 0.8 cm. On section, it had a brownish gray mottled appearance, with a soft hemorrhagic circumscribed area 0.6 cm. in diameter. Microscopic examination of this area showed it to be a small chromophobic adenoma.

Several small foci of terminal bronchopneumonia were scattered through the lower lobes of both lungs, more marked in the right. This observation was verified

5. Talbott, J. H.: Interpretations of Clinical Chemical Procedures, Ohio State M. J. **35**:137, 1939. Dill and Forbes.[5b]

TABLE 1.—*Experimental Observations on Blood*

| | | Whole Blood | | | | True Plasma, or Serum | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time, Hr. | Rectal Temperature, F. | Oxygen Capacity, Volume Per Cent | Oxygen Saturation, Per Cent | Total Carbon Dioxide, Volume Per Cent | Cell Volume, Per Cent | Total Base, m Eq. per Liter | Sodium, m Eq. per Liter | Potassium, m Eq. per Liter | Calcium m Eq. per Liter | Chloride, m Eq. per Liter | Phosphate, Mg. per 100 Cc. | Protein, Gm. per 100 Cc. | Lactate, Mg. per 100 Cc. | Urate, Mg. per 100 Cc. | Non-protein Nitrogen, Mg. per 100 Cc. | Arterial $p_H$ | Comment |
| 0 | 98 | 19.3 | 100.0 | 46.5 | 45 | 150.0 | 136.8 | 4.2 | 4.7 | 105.1 | 2.3 | 6.5 | .... | 2.3 | 24 | 7.37 | Arterial blood |
| 7 | 96 | 21.1 | 98.8 | 38.0 | 50 | 147.5 | 136.5 | 4.4 | ... | 101.5 | ... | 7.2 | 19.1 | 10.2 | .. | 7.31 | Arterial blood |
| 21 | 82 | 22.2 | 100.0 | 33.8 | 54 | 146.0 | 137.0 | 4.5 | 4.3 | 102.8 | 3.8 | 7.3 | 56.1 | .... | 40 | 7.28 | Arterial blood |
| 35 | 80 | .... | ..... | .... | .. | 150.5 | 137.8 | 5.4 | ... | ..... | 6.1 | 7.1 | .... | 10.5 | 55 | .... | Venous blood |
| 45 | 86 | 23.3 | 93.8 | 17.5 | 52 | 148.5 | 136.3 | 4.0 | 3.8 | 100.0 | 5.0 | 6.2 | 23.0 | 12.6 | 60 | 7.22 | Arterial blood |
| 48 | 89 | .... | ..... | .... | .. | 150.5 | 134.5 | 4.8 | 4.0 | 105.1 | ... | ... | .... | 11.5 | 70 | .... | Venous blood |

by microscopic examination, which revealed scattered alevoli filled with polymorphonuclear leukocytes and a few red cells.

The heart weighed 300 Gm. and was normal except for a small patent foramen ovale and slight atheromatous thickening of the aortic cusp of the mitral valve. Both coronary arteries showed moderate atheromatous changes, without appreciable narrowing of the lumens. Such changes also occurred in the aorta, with some calcification in the abdominal portion.

The kidneys weighed 200 Gm. and, except for slight arteriosclerotic changes consistent with the patient's age, were normal. There was slight hemorrhagic cystitis.

The thyroid, liver, spleen, pancreas and adrenal glands were normal, both grossly and microscopically.

The morphologic diagnoses included terminal bronchopneumonia, moderate sclerosis of the aorta and coronary arteries and slight renal arteriosclerosis, hemorrhagic cystitis and chromophobic adenoma of the pituitary gland.

TABLE 2.—*Chemical Constituents of Tissue*

| Tissue | Water, Gm. per 100 Gm. of Tissue | Sodium, mEq. per Kg. of Water | Potassium, mEq. per Kg. of Water | Calcium, mEq. per Kg. of Water |
|---|---|---|---|---|
| | | Patient W. D. | | |
| Psoas muscle | 77 | 29 | 141 | 8 |
| Heart | 79 | 40 | 116 | 3 |
| Liver | 73 | 72 | 84 | 4 |
| Kidney | 79 | 72 | 79 | 5 |
| Brain | 78 | 77 | 106 | 8 |
| | | Normal Subjects [20] | | |
| Muscle | 79 | 29 | 118 | 5 |
| Heart | 77 | 110 | 83 | 7 |
| Liver | 79 | 104 | 70 | 8 |
| Kidney | 80 | 90 | 56 | 13 |
| Brain | 90 | 83 | 94 | 7 |

## COMMENT

The descriptions in the available literature of the morphologic changes associated with hypothermia fall into one of three classes: those concerned with (1) animals which have been exposed experimentally to cold and in which temperature in many instances has reached lower levels than are observed in human subjects; (2) human beings who have been exposed accidentally to the cold, as sometimes happens during alcoholic intoxication, and many of whom have had one or more extremities frozen, and (3) human subjects in whom hypothermia has been induced for the treatment of extensive or metastatic malignant growths. It is apparent that under none of these conditions can the effect of cold per se on previously healthy tissue be ascertained. The report of Smith [6] is the closest approach that we

6. Smith, L. W.: Pathologic Changes Observed in Human Tissues Subjected to Subcritical Temperatures, Arch. Path. **30**:424 (July) 1940.

have discovered to the uncomplicated effect of cold on normal tissue. He has had opportunity in recent years to study the pathologic changes in 60 patients who have undergone one or more hypothermal treatments. He concluded that the action of cold, within the range studied, produced little morphologic alteration of normal tissue.

In this study we are concerned principally with the anatomic changes in the lungs, heart, kidneys and brain. Congestion of the lungs following exposure to cold has been observed in animals,[7] as well as in human beings.[8] Because of the prejudice that chilling predisposes to pneumonia it is important to evaluate as best we can this observation. None of the patients reported in the literature to have died after accidental exposure were thought to have had frank bronchopneumonia. Death was usually attributed to cardiac failure. During the past year we have supervised more than thirty hypothermal treatments. In all cases the patients were without clinical evidence of bronchopneumonia during or after the treatment and the roentgenograms of the chest were grossly normal also. The roentgen ray equipment permitted only a slow exposure, however, and fine pulmonary details were not evident. In none of the roentgenograms were large areas of consolidation visible.

Many patients with various types of cancer who were studied post mortem by Smith showed morphologic evidence of bronchopneumonia. He concluded, however, that in cases in which cancer was not a clinical terminal event the danger of fatal bronchopneumonia was negligible. In the case we report here the lungs showed patchy bronchopneumonia. It was the opinion of Dr. Benjamin Castleman, the pathologist, that it was not an overwhelming process and, other things being equal, was not extensive enough to cause death. At no time did our patient cough or raise bloody sputum.

The observed changes in the lungs were produced by at least two processes, i. e., slowing of the circulation and prolonged maintenance of the supine position. A slowing of the circulation is a secondary effect of peripheral vasoconstriction, expression of fluid from the vascular bed [9] and parenchymatous edema. The venous congestion of the lungs and interstitial edema may be identical to that observed by Walther [7a] in animals exposed to the cold. Impedance of gas exchange

7. (*a*) Walther, A.: Beiträge zur der Lehre von der thierischen Wärme, Virchows Arch. f. path. Anat. **25**:414, 1862. (*b*) Giese, E.: Experimentelle Untersuchung über Erfrierung, Inaug. Dissert., Jena, Berlin, L. Schumacher, 1901.

8. Nicolaysen, J.: Abrupt Fall in Body Temperature as the Result of Chilling, Norsk mag. f. lægevidensk. **5**:44, 1875. Smith.[6]

9. Benson, S.: Volume Changes in Organs Induced by the Local Application of External Heat and Cold and by Diathermy, Arch. Phys. Therapy **15**: 133, 1934.

across the alveolar membrane undoubtedly complicates the attempt of the organism to maintain homeostasis. Maintenance of the supine position during treatment is not ideal, but with the technic we employ at present it seems unavoidable. If cracked ice and a cold room, rather than especially constructed blankets, are available for induction, the position of the patient may be changed periodically and the untoward effect of hypostasis minimized.

It is concluded that while our patient had patchy areas of bronchopneumonia he did not die primarily because of them. Further evidence that fatal bronchopneumonia is not to be anticipated during or after hypothermia emanates from the observation that during periods of reduced temperatures practically complete bacteriostasis for ordinary pathogenic organisms exists.[6] Similar findings were reported by Chodounský [10] for animals. Two groups were exposed to virulent organisms. The control group was maintained at the usual environmental temperature and suffered a mortality of 63 per cent. The group that was chilled before exposure to the infectious agent, however, suffered a mortality of only 39 per cent.

A study of the morphologic changes in the heart is of great practical significance, since most patients who die after exposure suffer from terminal cardiac failure. The patient whose case is reported in this communication, as well as several studied by Smith, showed myocardial degeneration and atherosclerosis of the coronary vessels. It is to be doubted that hypothermia produces myocardial degeneration or coronary sclerosis. Hypothermia, however, imposes on the heart and blood vessels a severe burden, which they may be unable to withstand. This burden is produced by hemoconcentration, diminution in blood pressure and impaired oxygen transport.[3b] A temporary additional burden may appear periodically during restoration of body temperature. As the temperature is allowed to rise, by virtue of an increase in environmental temperature, peripheral vasodilatation is inevitable. With a rapid and sudden expansion of the vascular bed, the heart becomes inefficient in its ability to supply blood to the heart and brain. Usually this can be controlled. At the time our patient was studied the full significance of keeping vascular changes under control was not appreciated. When the patient went into circulatory collapse, because of peripheral dilatation, additional heat was applied to the skin and the vasomotor response was aggravated. With our present understanding of the physiologic changes which accompany hypothermia, cold rather than heat should have been applied. It is apparent that the mechanism of vasomotor collapse occurring during restoration of body temperature

10. Chodounsky, K.: Erkältung und Erkältungskrankheiten, Vienna, J. Šafař, 1907.

in hypothermia is quite different from that of vasomotor collapse occurring in surgical or medical shock.

The observations on heart size by roentgen ray examination and on cardiac function by electrocardiographic study require little discussion. It is debatable whether the progressive diminution in heart size during treatment is significant, but one can state definitely that no increase in diameter was noted. The electrocardiogram taken before hypotherma was within normal limits. The most marked changes were observed in the tracing taken thirty-four hours after induction of hypothermia and included slowing of the heart rate, elevation of the ST segments in leads I and II and lowering of the amplitude of the T waves in all leads. These abnormalities had in large part disappeared by the time the last tracing was taken.

We do not intend to imply that the cardiovascular system is the only one seriously affected by hypothermia. A disintegration of its function has been emphasized, because ominous consequences develop rapidly under stress. On the other hand, an alteration of the action of the kidneys, although less apparent, may be equally interesting. The presence of albumin in the urine in human beings following chilling [11] presumably is a physiologic response.[10] The development of albuminuria during hypothermia in animals,[12] as well as in human subjects, is probably a function of inadequate fluid intake. Albuminuria following dehydration may be observed in the absence of demonstrable renal damage; similarly its occurrence during hypothermia may be explained if the fluid intake is inadequate and the body is dehydrated.

Fluctuations in output of urine are related directly to fluid intake. If the intake is reduced, the hourly output is small; if the intake is large, the urine output is within the average range for normal subjects. A diminution in glomerular filtration and renal blood flow, however, has been an invariable accompaniment of hypothermia,[13] irrespective of fluid intake. The concentration of waste products in the serum during hypothermia has varied in our series. In the patient under discussion (table 1), the concentration of nitrogenous products and phosphate increased appreciably during treatment. Shortly before death, the nonprotein nitrogen was 70 mg. per hundred cubic centimeters and urate was 11.5 mg. per hundred cubic centimeters. Serum phosphate reached a maximum of 6.1 mg. per hundred cubic centimeters

11. Schlomka, G.: Untersuchungen über den Einfluss aüsserer Abkühlungen auf die Nierentätigkeit, Ztschr. f. d. ges. exper. Med. **61**:405, 1928.

12. (*a*) Zillessen, O. F. I.: Ueber Erkältung als Krankheitsursache, Inaug. Dissert., Marburg, 1899. (*b*) Lassar, O.: Ueber Erkältung, Virchows Arch. f. path. Anat. **79**:168, 1880. (*c*) Meyer-Lierheim, F., and Siegal, W.: Erkältung als Krankheitsursache, Ztschr. f. exper. Path. u. Therap. **9**:450, 1911. (*d*) Giese.[7b]

13. Unpublished data.

forty-five hours after hypothermia was induced and shortly before death had decreased to 5 mg. per hundred cubic centimeters. The combination of decreased glomerular filtration and dehydration, undoubtedly, can be held responsible for these high values. Therapeutically, it is believed that little can be done to increase glomerular filtration during hypothermia, but dehydration can be combated effectively by an augmented fluid intake.

No morphologic changes were noted in the kidneys at the postmortem examination of our patient. Few morphologic changes have been reported by others, either for animals or for human subjects. Giese [7b] found no significant anatomic variations in rabbits which had shown albuminuria before death. Zillessen,[12a] however, observed hyperemic glomeruli, areas of hyaline degeneration, cortical hemorrhages and hyaline and blood cell casts in the tubules. Smith [6] was unable to demonstrate evidence of renal damage in human subjects.

The brain and meninges are not excepted from morphologic alteration during hypothermia, and extensive studies of such changes may contribute to an understanding of the effects on the psyche observed during and after hypothermia.[3a] Nicolaysen,[8] Peter [14] and Bender [15] have reported congestion of the meninges and an increased amount of cerebrospinal fluid in persons frozen to death. In 3 human subjects, Fay [16] observed clinical evidence of cerebral edema after the body temperature returned to normal. In 1 spinal puncture showed a marked accumulation of fluid in the subarachnoid space. Evidence of cerebral edema was not apparent in our patient, although a few foci of cortical cell degeneration and fresh subependymal hemorrhages in the wall of the third ventricle were seen.

The other organs were essentially normal. The adrenal glands showed lipoid depletion. Meixner [17] expressed the belief that such a change was a direct result of hypothermia. Sano and Smith [18] did not agree. The other endocrine glands, the pituitary, the thyroid and parathyroids and the gonads, have been reported in the literature as normal. Thrombosis of the veins following exposure to the cold has been noted

14. Peter, M.: Des températures basses excessives, Gaz. hebd. de méd. et de chir. **9**:499, 1872.

15. Bender, L.: Lesions in the Brain in Death Caused by Freezing, Arch. Neurol. & Psychiat. **20**:319 (Aug.) 1928.

16. Fay, T.: Observations on Prolonged Human Refrigeration, New York State J. Med. **40**:1351, 1940.

17. Meixner, K.: Ein Fall von Tod durch Erfrieren, Deutsche Ztschr. f. d. ges. gerichtl. Med. **18**:270, 1931.

18. Sano, M. E., and Smith, L. W.: A Critical Histopathologic Study of Fifty Postmortem Cases of Cancer Subjected to Local or Generalized Refrigeration as Compared to a Similar Control Group of Thirty-Seven Non-Refrigerated Cases, J. Lab. & Clin. Med. **26**:443, 1940.

and is discussed in current literature as a frequent complication of freezing. It has been observed, however, only in vessels of frozen parts of the body [19] and not in parts that are not frozen. Thrombosis should not be considered as a complication of therapeutic hypothermia.

The small chromophobic adenoma within the pituitary gland was certainly noncontributory. It was not large enough to have altered the size of the sella turcica, as judged by roentgen ray examination. There was no clinical evidence that the patient was suffering from a adenoma of the pituitary body. It seems most unlikely that the adenoma was related to the patient's schizophrenia. Of some interest is the fact that the brain showed so few variations from normal. After eight years or profound mental disturbances only minimal demonstrable alterations in the morpologic structures were evident.

Several of the acid-base constituents of the blood in this patient (table 1), as well as in the other patients studied by us during hypothermia, have been discussed by Dill and Forbes.[3b] The concentration of hemoglobin in the blood in patient W. D. showed a progressive increase during treatment. The oxygen capacity increased from 19.3 to 23.3 volumes per cent and the cell volume from 45 to 52 per cent. The oxygen saturation of arterial blood remained normal. The values of 100 per cent for saturation are high and are assumed to be technical errors. The shift toward acidosis was marked. At the end of forty-five hours the total carbon dioxide content of arterial whole blood had decreased from 46.5 volumes per cent to 17.5 volumes per cent. This reduction, measured at body temperature, occurred despite the fact that in vitro alkaline reserve increases with decreasing temperatures.[3b] The lowest $p_H$ observed was 7.22. Four known factors contributed to the diminished alkaline reserve, as follow: 1. Hyperventilation occurred during most of the period of treatment. Since hyperventilation alone produces an increase in $p_H$, it must be assumed that other factors were operating which counteracted the hyperventilation alkalosis. 2. The concentration of lactate was increased. The maximum value noted was 56.1 mg. per hundred cubic centimeters. Restlessness and increased muscular activity were largely responsible for this, although a disturbance of intermediary metabolism of carbohydrate has not been excluded.[3b] 3. Phosphate and urate were retained. These changes have been discussed already. 4. The concentration of ketone bodies was increased. All specimens of urine contained acetone and ketone bodies. In summary, it may be stated that there are three major trends in the acid-base balance of patients during hypothermia,

19. Hodara, M.: Beitrag zur Histologie der Erfrierung, München. med. Wchnschr. **43**:341, 1896. Kriege, H.: Ueber hyaline Veränderungen der Haut durch Erfrierungen, Virchows Arch. f. path. Anat. **116**:64, 1889.

namely, concentration of blood, acidosis and retention of products usually excreted by the kidney.

In table 2 the data from the analyses of certain base constituents of tissue are compared with normal values.[20] In all tissues except heart muscle the concentration of water is less than normal. The sodium concentration is decreased and the potassium concentration increased in all. No constant change was noted regarding calcium. It is apparent that the tissues studied had lost water and sodium and had gained potassium. Depletion of interstitial fluid containing sodium and loss of cellular fluid leaving potassium behind could account for these variations.

## SUMMARY AND CONCLUSIONS

Morphologic and metabolic data are reported for a patient who died during experimental hypothermia. The patient had suffered from schizophrenia for more than ten years but was physically sound. During hypothermia a minimum rectal temperature of 80 F. was observed. The temperature remained below 98 F. for fifty hours. During restoration of temperature external heat was applied too rapidly. Cardiovascular collapse ensued, and death followed shortly. An autopsy was performed four hours later. The significant anatomic findings included patchy bronchopneumonia, slight degeneration of the cortical cells of the brain and a small adenoma of the pituitary gland. It is believed that none of the morphologic changes was independently responsible for death.

In retrospect it is thought that sudden vasodilatation was responsible for the cardiovascular breakdown. This change was aggravated by a combination of sluggish circulation, bronchopneumonia, impaired gas exchange in the lungs, acidosis and diminished glomerular filtration in the kidneys. Death, therefore, was produced by functional, rather than anatomic, disturbances.

It is concluded that prolonged hypothermia is without serious morphologic effect on normal tissue.

---

20. Shohl, A. T.: Mineral Metabolism, New York, Reinhold Publishing Corporation, 1939.

# THERAPY OF TETANUS

## A STUDY OF TWO HUNDRED AND SEVENTY-SIX CASES

RALPH SPAETH, M.D.
CHICAGO

In July 1933 a new routine for the treatment of patients with tetanus was introduced into the Cook County Hospital. In a previous publication [1] the rationale of this method of management has been discussed. This paper will be devoted to a description of the treatment employed and to a statistical analysis of the results noted in the care of 96 patients (referred to as the new series) managed according to the new routine during the seven year period ending in July 1940. Included as a basis for comparison is a discussion of the observations made from a detailed review of the hospital records of 180 patients (designated as the old series) treated according to the older routine during an eleven year period which preceded the introduction of the present method of management. Likewise, the general trend of the mortality from tetanus at Cook County Hospital has been reviewed for the years 1908 to July 1940 inclusive.

It is important to emphasize that the new technic stressed the centralization of control in the hands of a specially trained medical and nursing staff, which was drilled periodically in respect to the details of management. Practically all patients treated according to the new routine were placed under the care of special nurses during the major portion of their sojourn in the hospital.

### SEDATIVE THERAPY

Mild tetanus was encountered in patients free from convulsions, moderately severe tetanus in patients without cyanosis during tetanic spasms and severe tetanus in patients with cyanosis as an integral phase of the convulsive seizures. The two chief apparent dangers incident to convulsions were death from acute asphyxia and development of aspira-

---

From the Department of Pediatrics of the University of Illinois

The attending staff, the house physicians and the nursing staff of the Cook County Hospital gave constant cooperation and assistance. The Winthrop Chemical Company, Inc., supplied the avertin with amylene hydrate and Eli Lilly & Company the sodium amytal employed in this study.

1. Spaeth, R.: A Clinical Study of Tetanus, Am. J. Dis. Child. **60**:130-169 (July) 1940.

tion pneumonia. I did not investigate the incidence of compression fractures of the vertebrae, described by Dietrich.[2]

Although a dark, quiet environment and procedures to increase the patient's comfort were utilized, active sedative therapy was the keystone of treatment. Of the many sedative drugs discussed in the literature on tetanus, sodium amytal (sodium isoamylethylbarbiturate) and avertin with amylene hydrate (tribromethanol dissolved in amylene hydrate) were the ones used almost routinely since July 1933.

Both the nurses and the hospital physicians were permitted to administer sedative drugs for restlessness, painful spasticity of the skeletal muscles (neck, abdomen, trunk or extremities) or disturbing tonic spasms. Those in charge were instructed to use minimal effective doses in order to avoid depression of the cough reflex and the resultant danger of pneumonia. An attempt was made to keep the patient in a state of light to moderate narcosis until sedatives were no longer needed. The average patient required sedatives, usually in progressively diminishing amounts, for two or more weeks. When respiratory embarrassment occurred during convulsions, the attendants tried to determine whether the difficulty was caused by obstruction of the throat by secretions which could not be swallowed. Any such secretions were removed by mechanical means (see section on "General Management"), and cautious sedative treatment was then employed. Because the amount of sedative drug required proved to be a fairly reliable guide in formulating the prognosis, the nurses were instructed to make twenty-four hour summaries of the sedative therapy.

Printed instructions proved to be of considerable aid in facilitating treatment.[3] To the record of each patient was attached a table indicating the number of cubic centimeters of 2.5 per cent stock solution of avertin with amylene hydrate equivalent to 100, 50, 25, 15 and 10 mg. of tribromethanol per kilogram of body weight. The amount of sodium amytal corresponding to 5 mg. per kilogram of body weight [4] was found to be best expressed in milligrams, grains and cubic centimeters of 5, 10 and 20 per cent solutions, respectively.

---

2. Dietrich, H. F.: Tetanus in Childhood, Am. J. Dis. Child. **59**:693-710 (April) 1940.

3. These instructions have been considered in detail elsewhere.[1] On the routine forms, in addition to the data usually indicated, the following information is recorded: age; weight; previous serum or drug medication or idiosyncrasy; blood pressure; other diseases or complications (arteriosclerosis, edema, cachexia of any degree, acidosis, obesity, hepatic or renal disease).

4. Five milligrams per kilogram represents a dose corresponding to approximately 1/25 grain (2.6 mg.) of drug per pound (0.45 Kg.) of body weight. The 240 mg. dose is contained in the 3¾ grain ampule and 480 mg. in the 7½ grain ampule.

After an appropriate dose of avertin with amylene hydrate, given as a retention enema,[5] a sedative action ordinarily appeared in five to ten minutes. For the average patient with tetanus the initial dose was a volume of stock solution providing 25 mg. of tribromethanol per kilogram of body weight, followed at fifteen to thirty minute intervals with 10 to 15 mg. per kilogram, in accordance with the needs of each individual patient. This initial dose was raised to 40 or 50 mg. of tribromethanol per kilogram when severe convulsions were present and reduced to 15 mg. per kilogram when convulsions were either absent or mild. Three precautions were found to be important: (1) keeping an adequate supply of stock solution on the treatment tray; (2) testing the solution with congo red before each administration of the drug,[6] and (3) leaving the rubber tube in the rectum so that avertin with amylene hydrate could be administered without delay.

Sodium amytal was used alone or in conjunction with avertin with amylene hydrate. On the basis of past experience, an amount equivalent to 5 mg. per kilogram of body weight [4] was found to be a safe initial dose, with an upper limit of 240 mg.[4] for children and 480 mg. for adults. It was found desirable to try the effect of 240 mg. before resorting to a higher dose. The intramuscular injection of a 10 per cent aqueous solution, followed by additional doses at thirty to sixty minute intervals as needed, proved satisfactory for the patient with tetanus of average severity. Intravenous injections of a 5 to 10 per cent solution (1 cc. per minute—accurately timed!) were reserved for the control of alarming asphyxial spasms. The drug was given orally (dissolved in various pleasant vehicles) to those patients who were able to swallow, and it was administered rectally to those not in need of immediate narcosis but unable to swallow fluids with ease. Intravenous injections of sodium amytal induced the most prompt narcosis,[7] intramuscular administration a slower response and both oral and rectal treatment the slowest reactions.

Table 1 summarizes the sedative treatment employed for 52 patients of the new series.

I observed no clinical evidences of toxic injury to the various body organs among those patients who recovered after being treated with

5. Avertin with amylene hydrate is given only in the form of a retention enema, whereas sodium amytal can be administered by any of the available channels.[1]

6. When congo red is added to the stock solution, the appearance of a blue or violet color indicates the presence of a toxic dibromacetaldehyde, caused either by aging or by preparation of the solution with excessively hot water. Such material is not to be used. The test with congo red is dependable only when distilled water has been used as the diluent.

7. The intravenous injection is to be stopped as soon as the patient begins to show signs of drowsiness.

large doses of avertin with amylene hydrate or of sodium amytal. Likewise, no acquired resistance to either drug developed during the period of active treatment. However, in several of the patients who died convulsions persisted despite intensive therapy with sodium amytal or avertin with amylene hydrate. As might be anticipated, the more

TABLE 1.—*A Summary of Results of Treating Fifty-Two Patients with Tetanus by Means of Avertin with Amylene Hydrate and Sodium Amytal*

| | | Tribromethanol * | | | | | Sodium Amytal * | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age, Yr. | Weight, Kg. | Maximal Single Dose | Maximal Daily Dose | Average Daily Dose | Number of Days Given | Total Dose | Maximal Single Dose | Maximal Daily Dose | Average Daily Dose | Number of Days Given | Total Dose |
| **Patients Who Recovered** | | | | | | | | | | | |
| 12 | 40.9 | 50.0 | 321.0 | 245.6 | 17.0 | 417.6 | .... | .... | .... | .. | ..... |
| 12 | 37.0 | .... | ..... | ..... | .... | ..... | 6.5 | 58.3 | 26.7 | 8 | 214.0 |
| 8 | 25.0 | .... | ..... | ..... | .... | ..... | 7.7 | 53.7 | 21.5 | 10 | 215.0 |
| 8 | 24.0 | .... | .... | .... | .... | ..... | 10.0 | 40.0 | 28.0 | 5 | 140.0 |
| 5† | 16.3 | 25.0 | 152.0 | 115.6 | 7.0 | 809.0 | 14.7 | 29.4 | 17.6 | 5 | 88.3 |
| 55 | 81.8 | 68.8 | 310.5 | 173.8 | 10.0 | 1,738.0 | 5.8 | 8.8 | 5.8 | 2 | 11.7 |
| 7 | 22.7 | 20.0 | 415.0 | 179.4 | 25.0 | 4,489.0 | 10.5 | 31.6 | 15.4 | 10 | 154.3 |
| 5 | 20.4 | 25.0 | 292.0 | 162.0 | 17.0 | 2,765.0 | 11.7 | 11.7 | 11.7 | 2 | 23.4 |
| 9 | 31.8 | 25.0 | 174.0 | 101.5 | 8.0 | 812.0 | .... | .... | .... | .. | ..... |
| 15 | 39.5 | 56.0 | 278.0 | 139.5 | 14.0 | 1,954.0 | .... | .... | .... | .. | ..... |
| 4 | 15.9 | 40.0 | 230.0 | 134.8 | 11.0 | 1,483.0 | 15.1 | 30.2 | 30.2 | 1 | 30.2 |
| 46† | 68.2 | 20.0 | 125.0 | 74.7 | 17.0 | 1,270.0 | 7.0 | 21.1 | 11.3 | 13 | 147.8 |
| 49† | 68.2 | 20.0 | 151.0 | 94.6 | 10.0 | 946.0 | 7.0 | 21.1 | 14.9 | 13 | 193.7 |
| 18† | 63.6 | 25.0 | 135.0 | 63.8 | 21.0 | 1,342.0 | 7.6 | 22.7 | 6.1 | 12 | 73.7 |
| 11 | 36.3 | 23.0 | 354.0 | 205.7 | 13.0 | 2,674.0 | 6.6 | 26.4 | 18.6 | 11 | 204.5 |
| 13 | 38.2 | 15.0 | 262.0 | 125.5 | 11.0 | 1,380.0 | 6.2 | 36.4 | 24.0 | 19 | 457.4 |
| 7 | 20.0 | 25.0 | 365.0 | 235.3 | 12.0 | 2,824.0 | 3.2 | 6.4 | 6.4 | 4 | 25.6 |
| 43† | 65.9 | 20.0 | 200.0 | 111.8 | 12.0 | 1,341.0 | 7.2 | 7.2 | 5.8 | 3 | 17.4 |
| 8† | 27.3 | 35.0 | 217.0 | 112.2 | 22.0 | 2,469.0 | 17.5 | 17.5 | 13.0 | 4 | 52.1 |
| 10 | 29.5 | 25.0 | 200.0 | 116.6 | 12.0 | 1,405.0 | 4.3 | 10.8 | 9.7 | 3 | 29.2 |
| 34 | 75.4 | 25.0 | 241.0 | 131.0 | 7.0 | 916.0 | .... | .... | .... | .. | .... |
| 21 | 62.0 | 25.0 | 174.0 | 113.0 | 10.0 | 1,132.0 | .... | .... | .... | .. | .... |
| 45 | 63.0 | 50.0 | 194.0 | 161.0 | 8.0 | 1,288.0 | .... | .... | .... | .. | .... |
| **Patients Who Died** | | | | | | | | | | | |
| 10 | 30.5 | 78.0 | ..... | 199.2 | 2.5 | 498.0 | ... | .... | .... | .. | .... |
| 35† | 71.8 | 80.0 | 194.9 | 127.4 | 9.0 | 1,147.0 | 6.7 | 13.8 | 11.1 | 6 | 67.7 |
| 13 | 37.5 | 107.0 | ..... | 272.0 | 3.0 | 816.0 | ... | .... | .... | .. | .... |
| 6 | 18.2 | 80.0 | 563.0 | 487.3 | 55.0 | 2,680.0 | ... | .... | .... | .. | .... |
| 30 | 81.8 | 125.0 | 334.0 | 304.0 | 1.5 | 456.0 | ... | .... | .... | .. | .... |
| 13† | 43.2 | 30.0 | 177.0 | 177.0 | 1.0 | 177.0 | 5.5 | 44.0 | 37.0 | 1.5 | 55.5 |
| 41† | 65.9 | 25.0 | 200.0 | 188.0 | 2.0 | 375.0 | 7.2 | 21.8 | 21.8 | 1 | 21.8 |
| 7 | 25.0 | 45.0 | 351.0 | 296.0 | 4.0 | 1,185.0 | 9.6 | 19.2 | 19.2 | 1 | 19.2 |
| 11† | 36.4 | 50.0 | 371.0 | 371.0 | 1.0 | 371.0 | 6.6 | 6.6 | 6.6 | 1 | 6.6 |
| 3 | 13.6 | 60.0 | 221.0 | 248.0 | 2.0 | 497.0 | ... | .... | .... | .. | .... |
| 15 | 45.4 | 60.0 | 283.0 | 174.0 | 9.0 | 1,567.0 | ... | .... | .... | .. | .... |
| 42† | 77.3 | 60.0 | 306.0 | 268.3 | 3.5 | 939.0 | 3.1 | 3.1 | 3.1 | 1 | 3.1 |
| 56 | 72.7 | 60.0 | 116.0 | 155.3 | 1.5 | 233.0 | 4.9 | 9.9 | 9.9 | 1 | 9.9 |
| 20 | 63.6 | 58.0 | 196.0 | 202.6 | 1.5 | 304.0 | ... | .... | .... | .. | .... |
| 28 | 69.5 | 25.0 | 283.0 | 277.5 | 2.0 | 555.0 | ... | .... | .... | .. | .... |
| 6† | 22.7 | 20.0 | 137.0 | 137.0 | 1.0 | 137.0 | 10.5 | 10.5 | 10.5 | 1 | 10.5 |
| 2.5 | 11.4 | 25.0 | 155.0 | 88.5 | 2.0 | 177.0 | 22.0 | 84.2 | 84.2 | 1 | 84.2 |
| 26† | 72.7 | 25.0 | 305.0 | 295.5 | 2.0 | 591.0 | 6.6 | 16.5 | 16.5 | 1 | 16.5 |
| 19† | 54.5 | 25.0 | 82.0 | 69.3 | 1.5 | 104.0 | 8.8 | 8.8 | 8.8 | 1 | 8.8 |
| 8† | 25.0 | 25.0 | 292.0 | 260.0 | 1.5 | 390.0 | 9.6 | 19.2 | 19.2 | 1 | 19.2 |
| 13† | 65.9 | 20.0 | 55.0 | 61.0 | 1.5 | 92.0 | 7.2 | 7.2 | 7.2 | 1 | 7.2 |
| 19† | 59.1 | 20.0 | 241.0 | 145.6 | 8.0 | 1,165.0 | 4.0 | 24.3 | 24.3 | 1 | 24.3 |
| 50† | 65.9 | 10.0 | 86.0 | 67.0 | 2.0 | 134.0 | 3.6 | 25.4 | 12.7 | 2 | 25.4 |
| 60† | 70.5 | 10.0 | 56.7 | 56.7 | 1.0 | 56.7 | 3.4 | 20.4 | 20.4 | 1 | 20.4 |
| 36† | 45.2 | 20.0 | 135.0 | 106.5 | 4.0 | 426.0 | 5.5 | 33.3 | 25.9 | 5 | 129.6 |
| 17† | 60.4 | 15.0 | 250.0 | 175.4 | 5.0 | 877.0 | 7.9 | 11.9 | 10.7 | 6 | 64.6 |
| 32† | 47.7 | 25.0 | 258.0 | 246.6 | 1.5 | 370.0 | 10.0 | 10.0 | 10.0 | 1 | 10.0 |
| 6 | 25.0 | 25.0 | 350.0 | 248.7 | 4.0 | 995.0 | .... | .... | .... | .. | .... |
| 41 | 77.3 | 25.0 | 213.0 | 191.6 | 3.0 | 575.0 | .... | .... | .... | .. | .... |

* All doses are expressed in terms of milligrams per kilogram of body weight.

† Patients thus designated received both drugs on corresponding days during the major part of the illness. All others were given only one of the sedatives (at times with relatively small amounts of the other) during any given twenty-four hour period.

severely ill patients received the higher doses of the sedative drugs. This fact, among others, accounts for the observation that among the patients considered in table 1 approximately 35 per cent of those who died, in contrast to 10 per cent of those who recovered, had received single doses of avertin with amylene hydrate in excess of 50 mg. of tribromethanol per kilogram of body weight. In similar fashion, it explains why of the patients included in table 1, 42 per cent of those who died, in contrast to 15 per cent of those who recovered, had received

TABLE 2.—*An Analysis of Sedative Therapy for Two Hundred and Seventy-Six Patients with Tetanus*

| | | Intensity of Disease | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild | | Moderate | | Severe | | All Intensities | |
| | Sedatives | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death |
| Old series | Morphine sulfate alone *.... | 4 | .. | 1 | .. | 1 | 19 (2)† | 5 | 19 |
| | Morphine sulfate, chloral hydrate and bromides..... | 13 | .. | 6 | 3 | 1 | 23 (2) | 20 | 26 |
| | Morphine sulfate, chloral hydrate and phenobarbital..... | 3 | .. | 2 | .. | .. | .. | 5 | .. |
| | Morphine sulfate, chloral hydrate and magnesium sulfate..... | .. | .. | 1 | 1 | .. | 12 | 1 | 13 |
| | Chloral hydrate and bromides..... | 4 | .. | 5 | 1 (1) | 2 | 9 | 11 | 10 |
| | Miscellaneous ‡..... | 1 | .. | 6 | .. | .. | 5 (1) | 7 | 5 |
| | None or negligible..... | ? | .. | 5 | 3 (1) | 2 | 41 (2) | 14 | 44 |
| | Total..... | 32 | .. | 26 | 8 | 5 | 109 | 63 | 117 |
| New series | Avertin with amylene hydrate *..... | 6 | .. | 16 (1) | .. | 2 | 15 (9)§ | 25 | 15 |
| | Sodium amytal alone *..... | 6 | .. | 3 | .. | 3 (1) | .. | 12 | .. |
| | Avertin with amylene hydrate and sodium amytal* | 1 | .. | 10 | 1# | 5 (2) | 17 (12)‖ | 16 | 18 |
| | Miscellaneous ¶..... | 3 | .. | 1 | .. | .. | .. | 4 | .. |
| | None..... | 5 | .. | .. | 1 (1) | .. | .. | 5 | 1 |
| | Total..... | 21 | .. | 30 | 2 | 11 | 22 | 62 | 34 |

* For some patients negligible amounts of other sedatives were also used.

† The figure in parentheses indicates the number of patients with pneumonia.

‡ Magnesium sulfate, phenobarbital, codeine, barbital were used alone or in various combinations.

§ A 6 year old boy had bilateral bronchopneumonia and septic parotitis which did not respond to intravenous injections of sodium sulfapyridine and type-specific antipneumococcus serum.

# A 60 year old man had a markedly irregular heart for which digitalis was prescribed.

‖ A 19 year old woman had pneumonia, septic parotitis and a septic abortion. A 59 year old man had pneumonia, marked stomatitis and evidence of neglect preceding hospitalization. In a 41 year old man the blood gave chemical evidence of moderate nonprotein nitrogen retention (53.3 mg. of urea nitrogen and 3.3 mg. of creatinine per hundred cubic centimeters of blood).

¶ Phenobarbital, codeine, morphine and chloral hydrate were used alone or in various combinations.

an average daily dose of avertin with amylene hydrate in excess of 200 mg. of tribromethanol per kilogram of body weight. Although the data embodied in table 1 do not enable one to establish definitely the relation between the amount of sedation and the clinical outcome, observation of the patients impressed me with the thought that both overzealous and inadequate sedative treatments were to be avoided. It

appeared that the so-called happy medium had to be determined for each individual patient.

In table 2 data for the new series and the old series are compared in terms of the sedatives employed. Although table 2 is self explanatory, certain facts are worthy of emphasis. 1. Sedative therapy was of little importance, except from the standpoint of comfort, for those patients with mild forms of tetanus. Nevertheless, because of the difficulty of predicting the course of the disease, all patients with tetanus should receive routine sedation in accordance with individual needs. 2. Sodium amytal and avertin with amylene hydrate appeared to be definitely superior to the sedatives previously used for the treatment of moderate and severe tetanus. 3. In cases of severe tetanus, sodium amytal and avertin with amylene hydrate frequently failed to prevent death.[8] 4. Complications (pneumonia, septic parotitis) and associated pathologic conditions (septic abortion, cardiac abnormality, etc.) must be considered in comparing the recovery rates obtained in response to the different sedatives employed.

### SERUM THERAPY

Table 3 shows that tetanus antitoxin was administered to all except 13 patients. Serum treatment was omitted for 2 patients of the new series because they were convalescing at the time of hospitalization, and 11 patients of the old series died before antitoxin could be injected.

Tables 4 and 5 summarize the results of serotherapy.

In another publication [9] I have analyzed the foregoing data on a clinical and immunologic basis. The results of this analysis [9] indicated that a single dose of 30,000 American units probably represents an adequate amount of tetanus antitoxin for general use in all age groups.

---

8. Dietrich [2] has described favorable results in treating tetanus with seconal (sodium propylmethylcarbinylallylbarbiturate). The technic of seconal therapy has been presented by Breslow and Poncher (Use of Seconal in Pediatric Procedures, Illinois M. J. **80**:210-212 [Sept.] 1941). Curare and curarine have been used with some encouraging results in treating convulsions and spastic states (Melzner, E.: Experimentelle Untersuchungen über die Behandlung des Wundstarrkrampfes mit einer Kombination von Curarin und Avertin, Deutsche Ztschr. f. Chir. **212**:308-324, 1928. Cole, L.: Tetanus Treated with Curare, Lancet **1**: 475-477 [Sept. 1] 1934. Mitchell, J. S.: A Case of Tetanus Treated with Curarine, ibid. **1**:262-264 [Feb. 2] 1935. West, R.: Intravenous Curarine in the Treatment of Tetanus, ibid. **1**:12-16 [Jan. 4] 1936. Burman, M. S.: Therapeutic Use of Curare and Erythroidine Hydrochloride for Spastic and Dystonic States, Arch. Neurol. & Psychiat. **41**:307-327 [Feb.] 1939. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, J. A. M. A. **114**:322-324 [Jan. 27] 1940).

9. Spaeth, R.: Serum Therapy of Tetanus, with Special Reference to the Course of Antitoxin Titers in the Blood After Treatment with Specific Serum, Am. J. Dis. Child. **61**:1146-1174 (June) 1941.

TABLE 3.—*The Routes Employed for Administration of Antitoxin to Two Hundred and Seventy-Six Patients with Tetanus*

| Severity of Disease | Series | Unknown | | None | | Intrathecal * | | Intramuscular | | Intravenous | | Intramuscular and Intravenous | | All Routes | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death |
| Mild | Old | .. | .. | .. | .. | 29 | .. | .. | .. | .. | .. | 3 | .. | 32 | .. |
| | New | .. | .. | 2† | .. | .. | .. | 4 | .. | 6 | .. | 9 | .. | 21 | .. |
| Moderate | Old | 1 | 1 | .. | 1 | 24 | 6 | .. | .. | 1 | .. | .. | .. | 26 | 8 |
| | New | 1‡ | .. | .. | .. | .. | .. | 3 | 1 | 12 | .. | 14 | 1 | 30 | 2 |
| Severe | Old | .. | .. | .. | 10 | 4 | 78 | .. | 3 | .. | 4 | 1 | 14 | 5 | 109 |
| | New | .. | .. | .. | .. | .. | 1§ | 1 | .. | 7 | 20 | 3 | 11 | 11 | 32 |
| Total | Old | 1 | 1 | .. | 11 | 57 | 84 | .. | 3 | 1 | 4 | 4 | 14 | 63 | 117 |
| | New | 1 | .. | 2 | .. | .. | 1 | 8 | 1 | 25 | 20 | 26 | 12 | 62 | 34 |

* This category includes all patients who received antitoxin by the intraspinal or intracisternal routes, either alone or in combination with other channels.
† Convalescent patients, admitted on the fourteenth and the fifteenth day of the disease.
‡ The patient received 30,000 units by unstated routes over four days preceding hospitalization and was given 40,000 units intramuscularly on the day of admission to the hospital.
§ On the day of hospitalization the referring physician had administered 20,000 units intraspinally.

TABLE 4.—*The Average Doses of Antitoxin Employed in Treatment of One Hundred and Sixty-Nine Patients of Old Series with Tetanus*

| Intensity of the Signs of Tetanus | First 24 Hours | | | | First 48 Hours | | | | Entire Stay in Hospital * | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Recoveries | | Deaths | | Recoveries | | Deaths | | Recoveries | | Deaths | |
| | Patients | Dose† | Patients | Dose | Patients | Dose | Patients | Dose | Patients | Dose | Patients | Dose |
| Mild..... | 32 | 37,700 | .. | ..... | 32 | 48,200 | .. | ..... | 32 | 91,000 | .. | ..... |
| Moderate..... | 26 | 35,200 | 8 | 41,400 | 23 | 56,100 | 8 | 73,500 | 26 | 119,400 | 8 | 103,900 |
| Severe..... | 5 | 31,200 | 98 | 37,000 | 5 | 43,200 | 36 | 66,200 | 5 | 78,200 | 98 | 55,400 |
| All patients... | 63 | 35,800 | 106 | 37,400 | 60 | 50,800 | 42 | 56,800 | 63 | 101,700 | 106 | 58,100 |

* The average number of days of serum treatment was five and three-tenths for those patients who recovered and one and eight-tenths for those who died (the average duration of life among those who died was two and one-tenth days).
† Serum had been injected by a number of routes (table 3). All doses are expressed in units.

TABLE 5.—*The Relation Between Dose of Antitoxin * and Clinical Outcome for Ninety-Two Patients of New Series Given All Serum Intramuscularly or Intravenously*

| Dose of Antitoxin, Thousands of Units | Intensity of Disease | | | | All Intensities | | |
|---|---|---|---|---|---|---|---|
| | Mild to Moderate | | Severe | | | | |
| | Recovery | Death | Recovery | Death | Recovery | Death | Recovery Death |
| 100,000 | 9 (1)† | 1 | 2 | 6 (4)‡ | 11 | 7 | 1.5 |
| 81,000-90,000 | 1 | .. | .. | .. | 1 | .. | ... |
| 71,000-80,000 | 9 (1) | .. | 6 (2) | 5 (4)§ | 15 | 5 | 3.0 |
| 61,000-70,000 | 2 | .. | 1 | .. | 3 | .. | ... |
| 51,000-60,000 | 9 | .. | 2 | 12 (7) | 11 | 12 | 0.9 |
| 41,000-50,000 | 3 | 1 (1) | .. | 1 (1) | 3 | 2 | 1.5 |
| 31,000-40,000 | 11 | .. | .. | 7 (4) | 11 | 7 | 1.5 |
| 21,000-30,000 | 2 | .. | .. | .. | 2 | .. | ... |
| 20,000 | 2 | .. | .. | .. | 2 | .. | ... |

* All antitoxin was injected during the first twenty-four hours of hospitalization, except in the cases of 2 patients who received the total amounts over two to three days. Only 1 death occurred among the 17 patients first given serum after the fourth day of the disease.
† The figure in parentheses indicates the number of patients with pneumonia.
‡ A 60 year old man had a markedly irregular heart, and a 19 years old woman had septic parotitis, pneumonia and a septic abortion.
§ A 6 year old boy had septic parotitis and pneumonia, and a 50 year old man had pneumonia, marked stomatitis and evidences of extreme deprivation and neglect.

In order to allow a liberal margin of safety, a dose of 60,000 units was considered satisfactory for patients admitted to the hospital for serotherapy during the first five days of the disease and 40,000 units for mildly to moderately ill patients first treated later (see section on "results"). The analysis [9] further indicated that single doses of these magnitudes, administered by the intravenous or the intramuscular route, were associated with antitoxin titers which were adequate, both in level and in duration, to meet the indications imposed by a rational method of specific serotherapy.

As noted in table 3, intrathecal serotherapy was emphasized in the old series and intravenous and intramuscular serotherapy in the new series. The percentage distribution of patients of the old series and of the new series, respectively, in terms of the routes of serotherapy was: (1) intrathecal, alone or with other channels, 78.3 and 1.0; (2) intravenous, with or without the intramuscular route, 12.8 and 86.4 and (3) intramuscular alone, 1.7 and 9.4. Seven patients (3.9 per cent) in the old series received antitoxin intracisternally.

Among those patients of the old series given intrathecal serotherapy, the following results were noted: 1. Fifty-seven (40.4 per cent) of 141 patients recovered. 2. All of the 29 patients with mild forms of tetanus recovered. 3. Among those with moderately severe illness 24 (80 per cent) of 30 recovered. Intrathecal serotherapy obviously contributed directly to the unfavorable outcome for 2 patients who died. One of these patients was first hospitalized and given specific serum by the intramuscular and intravenous routes on the ninth day of his illness. The intraspinal injection of 20,000 units of tetanus antitoxin on the following day was succeeded by the rapid onset of marked generalized rigidity and convulsions, and the patient died on the eleventh day of illness. Severe convulsions developed in the other patient promptly after the intraspinal administration of 40,000 units, and the patient died ten hours after admission to the hospital. 4. Of the patients who were severely ill, only 4 (4.5 per cent) of 82 recovered. Intraspinal treatment apparently initiated convulsions in at least 5 of those who died. Another patient presented a picture of shock after the intracisternal injection of tetanus antitoxin on the fifth day of hospitalization (fourteenth day of tetanus) but ultimately recovered. 5. Apparently death could be caused by spinal or cisternal punctures per se. Acute, fatal asphyxial spasms occurred in 3 patients during the performance of spinal punctures and in 1 patient during the introduction of a needle into the cistern. In summary, the evidence would indicate that cisternal and spinal punctures and the introduction of antitoxin into the subarachnoid spaces may be classified as adverse environmental disturbances, which may be tolerated by the mildly to moderately severely ill patients but not by those with more severe forms of tetanus.

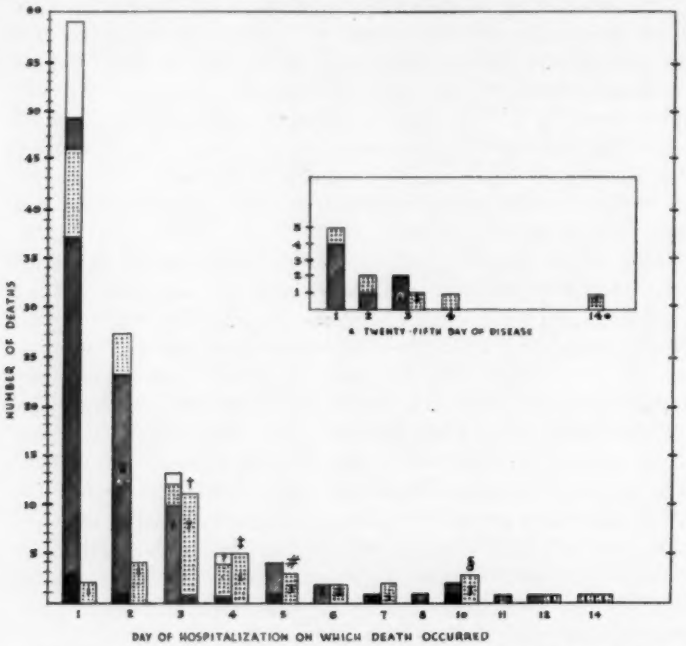
When antitoxin was introduced intravenously, either alone or in combination with intramuscular injection, the following results were noted: 1. Five (21.7 per cent) of 23 patients of the old series and 33 (61.4 per cent) of 83 patients of the new series recovered. 2. All of those with mild forms of tetanus recovered. 3. Among the patients with moderately severe tetanus only a single death occurred, 27 (96.4 per cent) of 28 patients of this group having recovered. 4. Recovery occurred in only 1 (5.3 per cent) of 19 severely ill patients of the old series, in contrast with 10 (24.4 per cent) of 41 patients of the new series. Intravenous serotherapy apparently caused no deaths and did not in any recognized instance adversely influence the ultimate clinical status of the patients thus treated.

Obviously, the limited number of patients given serum exclusively by muscle precludes any conclusions concerning the value of this type of management. Aside from the fact that all 3 of the severely ill patients of the old series died, and only 1 of 5 patients of the new series (4 moderately ill, 1 severely ill), it is of interest that 1 severely ill patient of the new series recovered after receiving a single intramuscular injection of 80,000 units. If one compares the intravenous and the intramuscular route for serum therapy in terms of safety, equipment and time required, degree of technical skill needed and relative speeds of absorption, the advantages of the former route are more theoretic than real. It is to be emphasized, however, that rapid absorption after intramuscular injection is facilitated by using the muscles on the anterolateral aspect of the thigh (not the gluteal region!) and possibly by giving one half of the total dose on each side.

In the chart I have analyzed the fatalities in terms of the day of hospitalization and the day of serum treatment [10] on which death occurred, the route employed for the administration of tetanus antitoxin and the incidence and character of complications which might have contributed directly to the unfavorable outcome. It is of interest that approximately 50 per cent of the deaths in the old series occurred during the first day of hospitalization, 23 per cent on the second, 11 per cent on the third and the rest on the fourth to the fourteenth day. It is significant that of the 59 patients who died on the first day in the hospital, 3 had been given serum exclusively by the intramuscular route and 10 had received no serum. In the latter group, death occurred from fifteen minutes to eight hours after hospitalization, apparently as a consequence of asphyxial spasms. At least 2 of these patients presented the clinical picture

10. The day of hospitalization for the treatment of tetanus corresponds to the day of serum treatment, except in the cases of 16 patients, 11 of whom received no antitoxin and 5 of whom received antitoxin after a delay of twenty-four hours or less.

described by Dietrich,[2] namely, coma, shock, rapid stertorous respirations and terminal disappearance of convulsions. I have observed the onset of similar clinical pictures in patients with tetanus who were sub-




The relation between the routes of serotherapy and the time of death for 145 patients with tetanus. The large chart includes all patients and the inset only those who were hospitalized for treatment after the fourth day of the disease.[10] The first column for any day or any single column represents patients of the series from 1921 to July 1933, and the second column represents patients of the series from July 1933 to July 1940. The routes by which antitoxin was administered are indicated as follows: solid black, intracisternal; diagonal lines, intraspinal (in some cases accompanied by injection through another route); dots, intravenous; horizontal lines, intramuscular; white space, no serum injected, and white space with a question mark, route not stated. A numeral enclosed in a part of a vertical column indicates the number of instances of pneumonia among patients given antitoxin by the corresponding route. The symbols on the large chart bear the following significance: †, a 59 year old man had pneumonia and stomatitis and showed evidences of marked neglect preceding hospitalization; ‡, a 41 year old man had blood which gave chemical evidence of moderate retention of nonprotein nitrogen (53.5 mg. of urea nitrogen and 3.3 mg. of creatinine per hundred cubic centimeters of blood), and a 60 year old man had a markedly irregular heart for which digitalis was prescribed; #, a 6 year old boy had septic parotitis and bilateral pneumonia which failed to respond to specific antipneumococcus serum and intravenous injections of sulfapyridine, and, §, a 19 year old woman had pneumonia, septic parotitis and a septic abortion.

jected to such environmental disturbances as venoclysis, noise and bathing. In respect to the time of onset of death, it is noteworthy that approximately 82 per cent of the deaths in the new series occurred on the third to the fourteenth day of hospitalization, that serum had been administered intravenously to all except 1 of the patients and that potentially fatal complications were present in 22 patients (65 per cent) of this series. These facts are pertinent because Dietrich [2] has pointed out that all of the 13 deaths in his series occurred within thirty-six hours of intraspinal or intravenous serum treatment. In summary, therefore, the evidence as presented by the patients treated at the Cook County Hospital, as well as elsewhere,[1] indicates that intrathecal, but not intravenous, serum treatment may occasion the alarming clinical pictures described by Dietrich.[2] Nevertheless, the possibility of ill effects from intravenous serotherapy (including acute reactions of an allergic character) must not be dismissed, and the probable adequacy of intramuscular serum treatment is deserving of more widespread study.

For intravenous administration, the antitoxin was poured into a flask containing 500 to 1,000 cc. of diluent (5 per cent dextrose in physiologic solution of sodium chloride or in Hartmann's solution [sodium lactate in Ringer's solution, available commercially]) and was allowed to flow at a rate of about 60 drops per minute.[11] With but occasional exceptions, sensitivity tests were omitted.[12] The vast majority of the patients of the new series received, about thirty minutes before the antitoxin, a hypodermic injection of atropine sulfate and epinephrine hydrochloride (1:1,000), in accordance with the following schedule of doses:

| Drug | Age of Patient | | | |
|---|---|---|---|---|
| | 6 Mo. | 2 Yr. | 5 Yr. | Adult |
| Epinephrine hydrochloride (1:1,000) | 3 minims (0.18 cc.) | 4 minims (0.25 cc.) | 5 minims (0.31 cc.) | 8 minims (0.49 cc.) |
| Atropine sulfate | 1/500 grain (0.12 mg.) | 1/250 grain (0.24 mg.) | 1/200 grain (0.3 mg.) | 1/100 grain (0.6 mg.) |

A syringe containing 1 cc. of epinephrine hydrochloride (1:1,000) was always available to treat any acute serum reaction. On certain occasions, 0.5 to 1.0 cc. of epinephrine hydrochloride (1:1,000) was poured into the solution of antitoxin.

11. Suggestions for a routine of serotherapy have been presented elsewhere.[1] The desirability of immersing the bottle of serum for about fifteen minutes in lukewarm water (not above 100 F. [37.7 C.]) has been pointed out by Hoyne (personal communication to the author) and the dangers incident to the use of improperly heated serum have been stressed (Hoyne, A. L.: The Pharmacopeia and the Physician: Immunologic Methods in Pediatrics, J. A. M. A. **112**:1581-1584 [April 22] 1939).

12. A complete discussion (theory and practice) of this problem has been presented in a previous publication.[1]

When patients in the new series received antitoxin both by muscle and by vein, from one half to two thirds of the total dose was given by the latter route and one half of the total intramuscular dose was injected into the muscles on the anterolateral aspect of each thigh on the theory that absorption would be more rapid from two intramuscular depots than from one.

In 5 patients of the new series acute reactions occurred after the intravenous injection of 40,000 to 60,000 units of antitoxin. In the old series such reactions appeared in 2 patients after the intravenous administration of 4,000 and 20,000 units, respectively.[13] Chills occurred in 2 patients, convulsions in 2, urticaria in 4, shock in 1, dyspnea in 4, nausea in 1 and fever (with a temperature of 104 to 105 F.) in 2. Of those with acute reactions, 1 patient in each series died. In neither instance, however, could the death be attributed to the acute reaction.[14] The reactions were treated in accordance with accepted methods, namely, injections of epinephrine hydrochloride (1:1,000), elevation of the foot of the bed, maintenance of body warmth by the use of blankets and other safe sources of external heat and control of cyanosis and apnea by artificial respiration, inhalation of oxygen and respiratory stimulants as indicated.

In the new series, in 18 of 69 patients (7 deaths) who lived seven or more days after their first serum treatment, serum sickness developed five to thirteen days later. The records indicate that 19 of 63 patients[15] of the old series who recovered showed signs of serum sickness six to fourteen days after the first injection of antitoxin. Twenty-eight (75.7 per cent) of all the late reactions appeared six to ten days, 5 (13.4 per cent) four to five days and 4 (10.9 per cent) eleven to fourteen days after the first dose of serum. Tables 6 and 7 reveal the following facts: 1. In the old series the incidence of late serum sickness showed yearly variations from zero to 85.7 per cent. In the new series the incidence during the period after January 1937 was approximately one-third that noted during the preceding three and one-half years and about one-half that recorded for the interval described in table 6. One can merely con-

13. Two other patients who died (1 after 300, and the other after 2,000, units of tetanus antitoxin had been administered intravenously) were not listed as dying of anaphylaxis, because the acute asphyxial spasms of tetanus obviously were responsible for the unfavorable outcomes.

14. The death in the new series was that of a 6 year old boy, who died of bronchopneumonia. Wheals and dyspnea developed in a 15 year old boy (old series) shortly after the intravenous injection of 4,000 units, but apparently he died of inadequately treated tetanic spasms (tetanus!).

15. In only 7 of the fatal cases in the old series did the patient survive the minimal period during which delayed serum sickness ordinarily occurs. For this reason, only the recoveries have been considered in this analysis.

jecture concerning the extent to which the use of more highly refined serum caused this lowered incidence. 2. Only 1 of 8 patients given antitoxin by muscle, in contrast to 17 of 52 who received it by vein (table 7), experienced a late serum reaction. Although this is suggestive, the limited number of cases does not warrant the conclusion that intramuscular serotherapy reduces the incidence of late serum sickness.

TABLE 6.—*The Occurrence of Delayed Serum Reactions Among the Sixty-Three Patients of the Series from 1921 to July 1933 Who Recovered* *

| | 1921 | 1922 | 1925 | 1926 | 1927 | 1928 | 1929 | 1930 | 1931 | 1932 | 1933† | Entire Period |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients..... | 10 | 11 | 8 | 2 | 3 | 5 | 4 | 5 | 3 | 7 | 5 | 63 |
| Reactions..... | 2 | 2 | 2 | .. | 1 | .. | 1 | 3 | 1 | 6 | 1 | 19 |
| Percentage..... | 20.0 | 18.2 | 25.0 | .. | 33.3 | .. | 25.0 | 60.0 | 33.3 | 85.7 | 20.0 | 30.1 |

* The average dose of antitoxin was 101,700 units. Fifty-nine of the 63 patients received over 40,000 units, and only 4 received less than this dose. Fifty-seven had received serum by the intraspinal route alone or in combination with other routes, 5 by the intravenous route alone or in conjunction with the intramuscular route and 1 by a route not described in the hospital record.

† January to July, inclusive.

TABLE 7.—*The Occurrence of Delayed Serum Reactions Among Sixty Patients of the Series from July 1933 to July 1940 Who Recovered*

| Total Dose, Units | Route | July 1933 to December 1936 | | | January 1937 to July 1940 | | | Entire Period of Study | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Patients | Reactions | Percentage | Patients | Reactions | Percentage | Patients | Reactions | Percentage |
| Over 40,000 | Intravenous | 19 | 10 | 52.6 | 26 | 3 | 11.5 | 45 | 13 | 28.8 |
| | Intramuscular | .. | .. | .... | 2 | 1* | 50.0 | 2 | 1 | 50.0 |
| | Total..... | 19 | 10 | 52.6 | 28 | 4 | 14.8 | 47 | 14 | 29.8 |
| 40,000 or less | Intravenous | 3 | 2 | 66.6 | 4 | 2 | 50.0 | 7 | 4 | 57.1 |
| | Intramuscular | 3 | .. | .... | 3 | .. | .... | 6 | .. | .... |
| | Total..... | 6 | 2 | 33.3 | 7 | 2 | 28.5 | 13 | 4 | 30.7 |
| All doses | Intravenous | 22 | 12 | 54.5 | 30 | 5 | 16.6 | 52 | 17 | 32.7 |
| | Intramuscular | 3 | .. | .... | 5 | 1 | 20.0 | 8 | 1 | 12.5 |
| | Total..... | 25 | 12 | 48.0 | 35 | 6 | 17.1 | 60 | 18 | 30.0 |

* Sixty thousand units was administered intramuscularly.

3. The data contained in tables 6 and 7 do not enable one to establish any relation between the total dose and routes of serotherapy, on the one hand, and the incidence of late serum sickness, on the other.

The exacerbation of convulsions in 3 patients at the time of late serum sickness called attention to the importance of adequate treatment of the discomfort by topical application of antipruritic agents, supplemented by the oral administration of ephedrine compounds (ephedrine-amytal and ephedrine-seconal capsules are commercially available) and parenteral injections of epinephrine hydrochloride (1:1,000) as indicated.

### TREATMENT OF THE LOCAL LESIONS

Tables 8 to 10 represent a study of the relation of the type of treatment of the local lesion to the respective mortality rates. They all show that no remarkable or consistent relation existed between the method of management of the local lesion and the clinical outcome. Those instances

TABLE 8.—*The Relation of the Care of Local Lesions and Mortality*

| | Old Series (1921 to July 1933) | | New Series (July 1933 to July 1940) | |
|---|---|---|---|---|
| | Recovery | Death | Recovery | Death |
| **No surgical intervention** | | | | |
| Hot compresses (boric acid or plain) | 8 | 8 | 17 | 12 |
| Cleansing of wounds, with or without local application of antiseptics * | 2 | 10 | 3 | 4 |
| Antiseptic dressings or irrigations † | 5 | 7 | 2 | 2 |
| Sulfanilamide, parenterally (abortion) | .. | .. | 1 | .. |
| Dry heat (gangrene of feet) | .. | 1 | .. | .. |
| Total | 15 (63.4)‡ | 26 | 23 (43.8) | 18 |
| **Surgical intervention** | | | | |
| Drainage of purulent collections | 3 | 8 | 2 | .. |
| Removal of splinters and slivers | .. | 5 | 3 | .. |
| Extraction of bullet | .. | 1 | .. | .. |
| Exploration of suspected lesion, with or without local application of antiseptics * | 7§ | 0 | 1 | 2 |
| Removal of surface of wound, with or without local application of antiseptics * | .. | .. | 2 | .. |
| Treatment of compound fractures | .. | 2 | .. | .. |
| Miscellaneous procedures | 2# | 4‖ | .. | 1¶ |
| Total | 12 (70.7) | 20 | 8 (27.3) | 3 |
| **No treatment recorded** | | | | |
| Lesion absent or indeterminate | 10 | 7 | 7 | 3 |
| Partial or complete healing of lesion noted | 15 | 10 | 18 | 3 |
| Innocent-appearing lesion | 7 | 3 | 6 | 2 |
| Lesion relatively inaccessible | 2** | 3†† | .. | .. |
| Exceedingly rapid onset of death | .. | 30 | .. | 1 |
| Reasons not apparent | 2 | 9 | .. | 4 |
| Total | 36 (63.3) | 62 | 31 (29.5) | 13 |

* The antiseptics used include tincture of iodine, boric acid, diluted solution of sodium hypochlorite U. S. P., hydrogen peroxide and ethyl alcohol.

† The antiseptics used include hydrogen peroxide, solution of potassium permanganate and diluted solution of sodium hypochlorite.

‡ The figure in parentheses represents the per cent mortality.

§ Concentrated phenol was applied locally in 1 case.

# The treatment for the 2 patients, respectively, was (a) wide resection of an infected abrasion, followed by cauterization with pure phenol, (b) resection of the gangrenous portion of an infected toe, followed by the application of dressings soaked with diluted solution of sodium hypochlorite.

‖ The treatment for the 4 patients, respectively, was (a) excision of an infected puncture wound; (b) drainage of an infected palmar lesion which followed a toy pistol wound, with postoperative cauterization with phenol; (c) removal of the necrotic tissue from gangrenous feet and legs, with the postoperative use of petrolatum gauze, compresses soaked with diluted solution of sodium hypochlorite and dry heat (heat cradle), and (d) debridement of an inflamed purulent wound of the leg.

¶ Treatment included the debridement of inflamed puncture wound of leg; probing of lesion; boric acid compresses.

** Appendectomy wound and abortion, respectively.

†† Herniotomy, cholecystectomy and hemorrhoidectomy, respectively.

in which operative treatment apparently reduced the mortality rate (for lacerations and cuts [table 9] and for severe tetanus among patients of the new series [table 10]) lack statistical significance because of the small number of patients available for study. Table 9 justifies the follow-

ing statements: 1. The mortality from penetrating wounds was high in the old series but not in the new. Lacerations and cuts caused a high mortality in both series. In the old series tetanus which occurred postoperatively and after compound fractures was associated with the highest

TABLE 9.—*The Relation of Local Lesions and the Type of Treatment to Mortality*

| Lesion | Series | Number of Patients | Percentage of All Patients | Number of Deaths | Percentage of All Deaths | Percentage Mortality | No Surgical Intervention | | Surgical Intervention | | No Treatment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Recovery | Death | Recovery | Death | Recovery | Death |
| Compound fracture | Old | 7 | 3.9 | 7 | 6.0 | 100.0 | ..... | 2 | ..... | 2 | ..... | 3 |
| | New | 1 | 1.0 | .. | ... | ..... | 1 | .. | ..... | .. | ..... | .. |
| Postoperative lesion * | Old | 6 | 3.3 | 5 | 4.3 | 83.3 | ..... | 2 | ..... | .. | 1 | 3 |
| Penetrating wound * | Old | 74 | 41.1 | 54 | 46.1 | 73.0 | 3 (70.0)† | 7 | 7 (74.1) | 20 | 10 (72.0) | 27 |
| | New | 27 | 28.1 | 7 | 20.5 | 25.9 | 4 (50.0) | 4 | 6 (14.3) | 1 | 10 (16.6) | 2 |
| Laceration or cut | Old | 32 | 17.8 | 22 | 18.8 | 68.7 | 2 (80.0) | 8 | 4‡ (43.0) | 3§ | 4 (73.3) | 11 |
| | New | 22 | 22.9 | 11 | 32.3 | 50.0 | 4 (55.5) | 5 | ..... | 2 | 7 (36.3) | 4 |
| Miscellaneous lesions * | Old | 24 | 13.3 | 15 | 12.8 | 62.5 | 5 (54.5) | 6 | ..... | 2 | 4 (61.6) | 7 |
| | New | 16 | 16.7 | 7 | 20.5 | 43.7 | 6 (45.4) | 5 | 1 | .. | 2 (50.0) | 2 |
| Superficial lesion * | Old | 13 | 7.2 | 5 | 4.3 | 38.4 | 3 | .. | 1 | 1 | 4 (50.0) | 4 |
| | New | 15 | 15.6 | 5 | 14.7 | 31.2 | 6 (33.3) | 3 | 1 | .. | 3 (40.0) | 2 |
| Lesion absent or indeterminate | Old | 17 | 9.4 | 7 | 6.0 | 34.2 | ..... | .. | ..... | .. | 10 (41.2) | 7 |
| | New | 10 | 10.4 | 3 | 9.0 | 30.0 | ..... | .. | ..... | .. | 7 (30.0) | 3 |
| Infection of unknown cause | Old | 7 | 3.9 | 2 | 1.7 | 28.5 | 2 | 1 | ..... | 1 | 3 | .. |
| | New | 5 | 5.2 | 1 | 3.0 | 20.0 | 2 | 1 | ..... | .. | 2 | .. |
| All lesions | Old | 180 | 99.9 | 117 | 100.0 | 65.0 | 15 (63.4) | 26 | 12 (70.7) | 29 | 36 (63.3) | 62 |
| | New | 96 | 99.9 | 34 | 100.0 | 35.4 | 23 (43.8) | 18 | 8 (27.3) | 3 | 31 (29.5) | 13 |

* Under this category are included the following lesions:

| | Old Series | | New Series | |
|---|---|---|---|---|
| | Recovery | Death | Recovery | Death |
| Penetrating wounds caused by | | | | |
| Nail | 9 | 22 | 12 | .. |
| Tack | .. | 2 | 1 | .. |
| Silver, splinter | 4 | 10 | 6 | 2 |
| Gunshot | 2 | 6 | .. | 1 |
| Blank cartridge | 1 | 11 | .. | .. |
| Firecracker | 3 | .. | 1 | .. |
| Fence picket | .. | .. | .. | 1 |
| Rusty wire | .. | .. | .. | 1 |
| Clothes hanger | .. | .. | .. | 1 |
| Cinder, gravel | .. | 2 | .. | 1 |
| Garden rake | 1 | .. | .. | .. |
| Unknown cause | .. | 1 | .. | .. |
| Superficial lesions | | | | |
| Scratch | 1 | 3 | 2 | 2 |
| Bruise | 6 | 1 | 7 | 3 |
| Blister | 1 | 1 | 1 | .. |

| | Old Series | | New Series | |
|---|---|---|---|---|
| | Recovery | Death | Recovery | Death |
| Postoperative lesions | | | | |
| Appendectomy | 1 | .. | .. | .. |
| Cholecystectomy | .. | 1 | .. | .. |
| Hernioplasty | .. | 1 | .. | .. |
| Hemorrhoidectomy | .. | 1 | .. | .. |
| Amputation of leg | .. | 1 | .. | .. |
| Reoperation, fracture | .. | 1 | .. | .. |
| Miscellaneous lesions | | | | |
| Burn | 2 | 5 | 3 | 1 |
| Osteomyelitis | .. | 1 | .. | .. |
| Carbuncle | .. | .. | .. | 1[c] |
| Furuncle | .. | 1 | .. | .. |
| Crushing injury | 5 | 4 | 4 | 2[b] |
| Gangrene (leg) | .. | 3 | 1 | 2 |
| Vaccination | 1 | 1 | .. | .. |
| Abortion | 1 | .. | 1[c] | 1 |

a. The patient was addicted to morphine, and the lesion was caused by repeated hypodermic injections.
b. In 1 case the injured leg had been amputated before the onset of tetanus.
c. Sulfanilamide was administered parenterally in treatment.
† The figure in parentheses represents the per cent mortality.
‡ Three patients had mild and 1 patient had moderately severe tetanus.
§ All patients had severe tetanus.

fatality rates. 2. The old series contained approximately 50 per cent more patients with penetrating wounds than did the new. On the other hand, the percentage incidence of superficial lesions (with relatively low

mortality) in the new series was twice that noted in the old. 3. For any type of treatment of specific local lesions, the mortality rates were consistently lower in the new series than in the old.

Table 10 indicates that the severity of the tetanus (enhanced by the presence of complications or other adverse conditions), and not the method of treatment of the local lesions, apparently determined the clinical outcome.

Personal observation of the patients of the new series stimulated the thought, previously entertained,[1] that surgical treatment of the local

TABLE 10.—*The Relation of the Severity of Tetanus and the Care of Local Lesions to Mortality*

| Severity of Tetanus | Series | No Surgical Intervention | | Surgical Intervention | | No Treatment | | All Treatments | |
|---|---|---|---|---|---|---|---|---|---|
| | | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death |
| Mild | Old | 5 | .. | 8 | .. | 19 | .. | 32 | .. |
| | New | 9 | .. | 1 | .. | 11 | .. | 21 | .. |
| Moderate | Old | 9 (10.0)* | 1† | 3 (40.0) | 2‡ | 14 (26.3) | 5§ | 26 (23.5) | 8 |
| | New | 10 (16.6) | 2# | 4 | .. | 16 | .. | 30 ( 6.2) | 2 |
| Severe | Old | 1 (96.1) | 25 | 1 (96.4) | 27 | 3 (95.0) | 57 | 5 (95.6) | 109 |
| | New | 4 (80.0) | 16 | 3 (50.0) | 3‖ | 4 (76.4) | 13 | 11 (74.4) | 32 |
| Total | Old | 15 (63.4) | 26 | 12 (70.7) | 29 | 36 (63.3) | 62 | 63 (65.0) | 117 |
| | New | 23 (43.8) | 18 | 8 (27.3) | 3 | 31 (29.5) | 13 | 62 (35.4) | 34 |

* The figure in parentheses represents the percentage mortality.

† A 47 year old man with an infected burn treated with diluted solution of sodium hypochlorite and boric acid solution (intraspinal serotherapy, inadequate sedation).

‡ A 5 year old boy from whose foot a piece of wood was removed (death during asphyxial spasm, intraspinal serotherapy) and a 48 year old man with an infected nail puncture wound of foot, which was opened twice while the patient was in the hospital (death from bronchopneumonia on the fifteenth day of hospitalization).

§ The lesions were absent in 1 patient, minor (superficial crusts) in 2, a healed puncture wound in 1 (wood removed before hospitalization) and a laceration in 1. The patients' ages were 78, 75, 63, 44 and 34 years. Pneumonia was noted in 2 patients (aged 78 and 34). Sedation was inadequate in 4, and 3 had received intraspinal serotherapy.

# A 39 year old man with superficial injuries of the hand treated with hot dressings (death on the fourteenth day of hospitalization, bronchopneumonia, history of chronic alcoholism), and a 60 year old man with gangrene of the feet treated by heat cradle (death on fourth day of hospitalization, markedly irregular heart which required digitalis therapy and history of treatment for syphilis).

‖ Includes a 6 year old boy with several lacerations treated by surgical exploration and boric acid compresses, and a 26 year old man with a laceration treated by incision and hot compresses.

lesions was not an immediate need. Under all circumstances, treatment of accessible wounds was instituted only after the patient had received adequate sedative and antitoxin treatment. This principle of management was accepted because it was learned that such disturbance in highly excitable patients could incite potentially fatal asphyxial spasms.[1]

The observations made in this investigation confirm the conclusions reached in my study [1] at the University Hospitals, Iowa City, namely, that the principles of surgery to be followed in the treatment of tetanus are identical with those to be recommended in the absence of this disease. The management of wounds must be adapted to the special requirements of each individual case. Under no circumstances is one justified in

resorting to amputation, excision of a local lesion or drainage of a purulent collection for the sole purpose of removing the focus at which toxin is being elaborated. Abel and Hampil [16] have cited evidence which indicates that such procedures do not influence the course of tetanus either in human beings or in animals after the disease has developed. Likewise, McClintock and Hutchings,[17] on the basis of critical animal experiments, concluded that amputation of an affected member at the first appearance of active symptoms of tetanus in no way altered the progress of the disease. The animals given surgical care died in the same time and with the same symptoms as those not surgically treated.

After the injection of appropriate amounts of specific serum, one may rely on circulating antitoxin to neutralize any toxin which may continue to be discharged from the point of infection. In the presence of a persistent focus of infection, the possibility of recurrences cannot be denied. For this reason, after acute signs and symptoms have been adequately treated, a gentle but careful search for foreign bodies is justified. Even though wounds appear healed, splinters or other extraneous material may be discovered by careful surgical exploration. However, if nail puncture wounds appear to be healed, surgical exploration does not seem necessary. In the presence of purulent collections, debridement, drainage and removal of any foreign bodies from all wounds are necessary. Irrigation with hydrogen peroxide, dilute solution of sodium hypochlorite (Dakin's solution), solution of potassium permanganate or some other oxidizing solution may aid in establishing free drainage and local repair. However, such procedures do not seem to affect the natural course of the tetanus intoxication.[18] Although amputations and other disfiguring operations are to be avoided as far as is feasible, if a structure is already hopelessly destroyed surgical removal is indicated. Gas gangrene must be treated as a special complication. It is perhaps timely to mention that injuries caused by aerial attacks on civilian or military populations will require the most skilful types of surgical management.

### GENERAL MANAGEMENT

As soon as tetanus was recognized, the patient was placed under the care of a specially organized tetanus team which consisted of a group of nurses and resident physicians who were instructed regularly concerning all the details of routine treatment. During the earlier part of the study

16. Abel, J. J., and Hampil, B.: Researches on Tetanus: IV. Some Historical Notes on Tetanus and Commentaries Thereon, Bull. Johns Hopkins Hosp. **58**:343-376 (Dec.) 1935.

17. McClintock, C. T., and Hutchings, W. H.: The Treatment of Tetanus, J. Infect. Dis. **13**:309-320 (Sept.) 1913.

18. Coleman, G. E.: Experimental Study of Tetanus, J. Infect. Dis. **47**:410-415 (Nov.) 1930.

(after July 1933) the patients were treated in their respective wards, later, in order to effect a greater degree of centralization, they were transferred to a special ward in the hospital. An adequate supply of printed instructions was available to guide the members of the hospital staff.

The general management of these patients was the same as that for the series treated at the University Hospitals [1] in Iowa City, and may be outlined as follows:

1. *Special Nursing Care.*—Special attendants may be released when the patient is able to walk or move around the sickroom in an invalid chair. In the absence of constant nursing care, patients may succumb to hypostatic pneumonia, dehydration, starvation, physical injuries or sudden fatal asphyxia. No patient who has had convulsions should be placed in a general ward until the danger of a delayed serum reaction, with a possible recurrence of convulsions, has passed (see section on "Serum Therapy").

2. *Maintenance of an Adequate Fluid and Caloric Intake.*—This requirement must be met with but minimal disturbance to the patient. It is much more important to keep the patient quiet than to meet theoretic metabolic needs. A diet high in carbohydrate is desirable. Attempts at feeding by any route should be abandoned immediately if they incite asphyxial convulsions. If the sedatives relieve the swallowing difficulty (trismus and pharyngeal spasms), a liquid or soft diet may be given orally. The food is to be offered at the onset of relaxation, and the patient is never to be awakened for feedings. Liquids should be fed literally drop by drop, by means of medicine droppers with attached rubber tubing. Some patients fare better with glass suction tubes, whereas others drink more easily with the ordinary infant's nursing bottle and nipple. In the presence of intractable difficulty in swallowing one may employ daily intravenous injections of 1,000 to 2,000 cc. of a 5 per cent solution of dextrose in Hartmann's buffered solution. If necessary, veins should be exposed at the ankle or the cubital fossa, with the region under local anesthesia. Except for the occasional convalescent patient with a markedly swollen tongue, nasal feedings should be avoided because of the danger of inciting asphyxial spasms. Transition to the regular diet should be gradual. Repeated transfusions from suitable donors may be of value in combating the associated inanition and possibly in assisting the immunologic defense mechanism.[19]

3. *Treatment of Constipation and Retention of Urine.*—These disturbances may be caused by hypertonicity of the sphincters and may incite acute abdominal discomfort, at times colicky and difficult of differentiation from the pain associated with tetanic contractions of the abdominal wall. If the pain is of gastrointestinal origin, relief may be obtained by the use of cleansing enemas and of atropine sulfate administered by mouth or by hypodermic injection. To prevent such difficulties, enemas may be required every other day. If distention of the urinary bladder occurs,[20] catheterization, followed by the instillation of a 1:5,000 solution

19. Seven patients (4 recovered and 3 died) received blood transfusions.

20. Retention of urine was recorded for 7 patients of the old series and for 11 of the new. Nine of these patients were children (3 to 14 years old) and the remainder were adults (26 to 59 years old). Seven patients (3 children) of the new series were catheterized on at least one occasion. Of those with urinary retention, death occurred in 5 patients of the old series and 2 of the new.

of potassium permanganate or some other appropriate antiseptic solution, is indicated.

4. *Measures to Prevent the Occurrence of Pneumonia.*—Procedures adapted to this purpose are as important as serum and sedative therapy. Prolonged rigidity of the thorax, with associated impairment of pulmonary ventilation, may be combated with adequate sedation supplemented by inhalations of 5 to 10 per cent carbon dioxide in oxygen. The inhalations are conveniently given for periods of ten to fifteen minutes at four hour intervals (or oftener if not too disturbing to the patient), but should be withheld if undue excitement is occasioned. A dorsal position should be avoided as far as is feasible by placing the patient on the abdomen or side as much as possible. Frequent tepid sponge baths, protection from drafts and moderate bed clothing reduce the danger of the pneumonia which

TABLE 11.—*Pertinent Data Concerning Thirty-Five Patients with Tetanus Complicated by Pneumonia*

| | Old Series | New Series | Total |
|---|---|---|---|
| Number of patients with tetanus | 180 | 96 | 276 |
| Number of patients with pneumonia * | 9 ( 5.0%) | 26 (27.1%) | 35 (12.7%) |
| Deaths among patients with pneumonia | 8 (88.8%) | 22 (84.6%) | 30 (85.7%) |
| Day of disease pneumonia first observed: | | | |
| 1st to 7th | 4 | 20 | 24 |
| After 7th | 4 | 4 | 8 |
| Unknown | 1 | 2 | 3 |
| Day of hospitalization pneumonia first observed: | | | |
| 1st to 7th | 9 | 24 | 33 |
| After 7th | .. | 1 | 1 |
| Unknown | .. | 1 | 1 |
| Age of patients in years: | | | |
| 15 or less | 4 | 13 | 17 |
| 16 to 30 | .. | 5 | 5 |
| 31 to 50 | 3 | 6 | 9 |
| Over 50 | 2 | 2 | 4 |
| Severity of the clinical picture of tetanus: | | | |
| Moderate | 2 | 1† | 3 |
| Severe | 7† | 25‡ | 32 |

* The following diagnostic criteria were employed: (a) clinical appearance in the absence of definite signs in the chest in 6 patients of the old series and in 14 of those in the new (in the latter group, the diagnosis for 3 of 4 of those who died was confirmed by necropsy and for 1 by roentgen examination during life; all showed bronchopneumonia) and (b) clinical appearance confirmed by typical physical signs in the chest in 3 patients of the old series and in 12 of those in the new.

† One patient recovered.

‡ Three patients recovered.

might otherwise follow excessive perspiration and chilling of the general body surface. To relieve the respiratory difficulty occasioned by collections of saliva or other secretions in the nasopharynx, ordinarily it is sufficient to wipe the patient's lips after he has been induced to blow out this material with the head or the whole body turned to one side. At times, mechanical suction, with minimal disturbance to the patient, is required. Elevation of the foot of the bed may possibly aid in directing secretions away from the lower part of the respiratory tract. Atropine sulfate is of little value as a means of preventing pulmonary complications. In fact, the secretions become thick and difficult to expectorate if this drug is employed.

Table 11 reveals that pneumonia was diagnosed for approximately one eighth of all the patients and that the apparent incidence in the new series was approximately five times that observed in the old. Because

of the short duration of life among the fatal cases of the old series and the limited number of necropsies, table 11 does not represent an exact comparison of the two series of patients in terms of this complication. In all likelihood, the incidence of pneumonia was much higher in the old series than the figures would indicate. It is of interest that in all except 2 instances the pneumonia occurred during the first week of hospitalization. The high incidence among children is of significance from the standpoint both of diagnosis and of treatment. Practically all those in whom pneumonia developed had severe forms of tetanus, and pulmonary involvement was not encountered among those with mild forms of the disease.

TABLE 12.—*An Analysis of the Clinical Outcome for One Hundred and Seventy-Seven Patients with Tetanus and Elevated Temperature*

| Apparent Cause of Fever | New Series | | Old Series | | Total | |
|---|---|---|---|---|---|---|
| | Recovery | Death * | Recovery | Death * | Recovery | Death |
| Pneumonia | 4 | 22† | 1 | 8 | 5 | 30 |
| Serum therapy | 4‡ | .. | 26 (25)§ | 2 | 30 | 2 |
| Local lesion | 2 | .. | .. | .. | 2 | .. |
| Preterminal | .. | .. | .. | 16 (10) | .. | 16 |
| Unknown | 7# | 9 | 11 (9) | 65 (47) | 18 | 74 |
| Total | 17 | 31 | 38 | 91 | 55 | 122 |

* Among those patients who died, the hospital records of 3 in the new series and of 26 in the old series, did not contain information in respect to body temperature.

† Two of these patients had septic parotitis (1 with an associated septic abortion), and a third (a 59 year old man) had marked stomatitis and signs of extreme physical neglect.

‡ In 3 of these patients the fever was associated with late serum sickness, and in 1 it was associated with an acute thermal reaction to an intravenous injection of 60,000 units of tetanus antitoxin (temperature, 104 F.). In the latter patient stomatitis prolonged the febrile period.

§ The figure in parentheses indicates the number of patients who received intratheeal serotherapy. One of the 25 patients here indicated had an acute serum reaction (temperature 105.4 F.) about fourteen hours after the intramuscular, intravenous and intraspinal injection of 50,000 units of antitoxin. A more protracted fever was apparently caused by a septic abortion present at the time of hospitalization.

# Two of these patients had received sulfapyridine orally on the first appearance of fever.

The high mortality rates recorded in table 11 reflect the ominous outlook of the pneumonia which occurred as a complication of tetanus in the era which preceded the introduction of specific chemotherapy and serotherapy. Although sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was used in the treatment of but 2 patients with pneumonia [21] and type-specific serum in the treatment of only 1,[21] it

21. A 6 year old boy died on the fifth day of his stay in the hospital despite the intravenous injection of 105 grains (6.89 Gm.) of sodium sulfapyridine during a period of about three days and of 145,000 units of type-specific (type not recorded on chart) antipneumococcus serum, given as four doses in two days. Recovery occurred in the case of an 8 year old girl with severe tetanus who received 100 grains (6.5 Gm.) of sodium sulfapyridine intravenously in approximately three days. The response to chemotherapy was spectacular. The patient appeared

would not seem illogical to anticipate that the early institution of chemotherapy and serotherapy [22] might reduce the fatality rate among patients with tetanus in whom pneumonic complications develop. In the presence of elevations in temperature of unexplained origin (table 12), the existence of pneumonia is to be suspected, and sulfapyridine should be administered even before typical pulmonary signs appear.[23] As noted in a footnote to table 12, such a policy was adopted in the care of 2 of the patients who recovered. Although this study does not warrant the presentation of any conclusions concerning the therapeutic value of oxygen [24] and the other measures employed in the treatment of pneumonia, it seems reasonable to propose that the pneumonia which occurs in a patient with tetanus should receive essentially the same type of management as that which occurs under other circumstances.

## RESULTS

Table 13 reveals four important facts. 1. The percentage incidence of mild tetanus was approximately the same in the old and in the new series (17.8 and 21.9 per cent, respectively), that of moderately severe tetanus in the new series was almost twice that in the old (33.3 and 18.8 per cent) and that of severe forms of the disease was about 20 per cent greater in the old series than in the new (63.3 and 44.8 per cent). One can merely speculate concerning the specific roles played by the different types of treatment in determining these relative degrees of severity of the disease. In all probability, however, the omission of intraspinal serotherapy contributed to this reduction in the incidence of severe forms of tetanus. 2. Although the mortality rates among patients with incubation periods of over ten days was about 18 per cent lower than among

---

to be in a terminal condition at the start of treatment, with rapid, grunting respirations accompanied by cyanosis. The temperature dropped from 104 to 100.5 F. in less than twenty-four hours, and the patient's illness pursued an essentially afebrile course thereafter.

22. Special precautions must be observed to avoid acute anaphylactic reactions because the patient usually has already received antitoxin containing horse serum. If the patient fails to respond to chemotherapy within twenty-four hours, treatment with homologous antipneumococcus serum should be contemplated.

23. Although fever and accelerated respirations should suggest a diagnosis of pneumonia, atelectasis and acidosis must be ruled out by the use of the necessary procedures.[1] Ketone bodies were detected in voided specimens of urine from 5 patients (1 of whom died). A sixth patient (who died) had a marked odor of actone on the breath, but had no recorded specimen of urine subjected to laboratory examination.

24. The fact that oxygen therapy was employed with variable degrees of thoroughness in this study precludes the presentation of any conclusions concerning the value of such treatment of the pneumonia which may occur as a complication of tetanus.

those with the shorter intervals, it is significant that mortality rates of 42 per cent in the old series and 24 per cent in the new were encountered among the patients with incubation periods of eleven or more days.[25] It is obvious, therefore, that a short incubation period justifies a more

TABLE 13.—*An Analysis of the Outcome for Two Hundred and Seventy-Six Patients with Tetanus, with Reference to Incubation Period and Duration of Symptoms Up to the Time of Hospitalization*

| | | | Incubation Period in Days | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | 10 or Less | | Over 10 | | Unknown | | All Periods | |
| Duration of Disease * | Severity of Disease | Series | Recovery | Death | Recovery | Death | Recovery | Death | Recovery | Death |
| Four days or less | Mild | Old | 9 | .. | 10 | .. | 5 | .. | 24 | .. |
| | | New | 4 | .. | 7 | .. | 2 | .. | 13 | .. |
| | Moderate | Old | 2 | 1 | 6 | .. | 4 | 1 | 12 | 2 |
| | | New | 14 | 1 (1)† | 6 (1) | .. | 1 | 1‡ | 21 | 2 |
| | Severe | Old | 1 | 61 (3) | 1 (1) | 24 (1) | .. | 12 (1) | 2 | 97 |
| | | New | 7 (1) | 21 (11)§ | 2 (1) | 6 (5) | 2 (1) | 3 (3) | 11 | 30 |
| | Total | Old | 12 | 62 | 17 | 24 | 9 | 13 | 38 | 99 |
| | | New | 25 | 22 | 15 | 6 | 5 | 4 | 45 | 32 |
| Five or more days | Mild | Old | 3 | .. | 2 | .. | 3 | .. | 8 | .. |
| | | New | 3 | .. | 4 | .. | 1 | .. | 8 | .. |
| | Moderate | Old | 4 | 2 | 3 | 1 (1) | 6 | 2 (1) | 13 | 5 |
| | | New | 3 | .. | 3 | .. | 3 | .. | 9 | .. |
| | Severe | Old | 2 | 1 | .. | 4 | 1 | .. | 3 | 5 |
| | | New | .. | .. | .. | 1 (1) | .. | .. | .. | 1 |
| | Total | Old | 9 | 3 | 5 | 5 | 10 | 2 | 24 | 10 |
| | | New | 6 | .. | 7 | 1 | 4 | .. | 17 | 1 |
| Not stated | Moderate | Old | 1 | .. | .. | .. | .. | 1 | 1 | 1 |
| | | New | .. | .. | .. | .. | .. | .. | .. | .. |
| | Severe | Old | .. | 2 | .. | 1 (1) | .. | 4 | .. | 7 |
| | | New | .. | .. | .. | .. | .. | 1 (1) | .. | 1 |
| | Total | Old | 1 | 2 | .. | 1 | .. | 5 | 1 | 8 |
| | | New | .. | .. | .. | .. | .. | 1 | .. | 1 |
| All patients | Mild | Old | 12 | .. | 12 | .. | 8 | .. | 32 | .. |
| | | New | 7 | .. | 11 | .. | 3 | .. | 21 | .. |
| | Moderate | Old | 7 | 3 | 9 | 1 | 10 | 4 | 26 | 8 |
| | | New | 17 | 1 | 9 | .. | 4 | 1 | 30 | 2 |
| | Severe | Old | 3 | 64 | 1 | 29 | 1 | 16 | 5 | 109 |
| | | New | 7 | 21 | 2 | 7 | 2 | 4 | 11 | 32 |
| | Total | Old | 22 | 67 | 22 | 30 | 19 | 20 | 63 | 117 |
| | | New | 31 | 22 | 22 | 7 | 9 | 5 | 62 | 34 |

* Antitoxin was administered on the day of hospitalization, except as follows: (a) a delay of twenty-four hours or less for 5 patients of the old series and (b) omission of serotherapy for 2 patients of the new series (mild disease) and for 11 of the patients of the old series (early death).

† The number in parentheses indicates the incidence of pneumonia.

‡ One patient had a remarkable irregular heart which failed to respond to treatment with digitalis.

§ Of those with pneumonia, 2 had septic parotitis (1 with an associated septal abortion), and 1 had marked stomatitis and evidences of neglect (59 year old man). A patient without pneumonia had nonprotein nitrogen retention.

25.

| | Incubation Period in Days | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 to 5 | 6 to 10 | 11 to 15 | 16 to 20 | 21 to 30 | 34 to 85 | Unknown | All Periods |
| Old series | 32 (29)* | 57 (38) | 31 (15) | 8 (5) | 9 (7) | 4 (3)† | 39 (20) | 180 (117) |
| New series | 14 (7) | 39 (15) | 17 (5) | 5 (1) | 7 (1) | — | 14 (5) | 96 (34) |

* The figures in parentheses indicate the number of deaths.

† The 3 patients who died had incubation periods of thirty-four, thirty-eight and fifty-six days, respectively.

serious prognosis than does one of greater duration. Nevertheless, it is apparent that for the individual patient with tetanus the incubation period is of limited prognostic value. 3. In both series the vast majority of the deaths occurred among those patients who sought medical care during the first four days of the disease (84.6 per cent in the old series and 94 per cent in the new). These figures reflect the greater incidence of severe tetanus among those hospitalized early than among the group admitted after the fourth day of the disease. For example, approximately 65 per cent of all patients admitted early, in contrast to about 17 per cent of those hospitalized later, had severe forms of tetanus. It is significant that essentially the same percentage of patients in the two series was admitted during the first four days of the disease, and it is noteworthy that the incidence of severe forms of tetanus among those hospitalized early was 19 per cent lower in the new series than in the old (53.2 and 72.2 per cent, respectively). In this respect it is to be restated that this lower incidence of severe tetanus represents a difference probably attributable to the omission of meddlesome types of serum treatment. On the other hand, it is important to emphasize that among those patients admitted during the first four days of the disease potentially fatal complications were recognized much more frequently in the new series than in the old. Thus, the diagnosis of pneumonia was made for 24 of 77 patients of the new series and only 6 of 137 patients of the old series. Likewise, if the two series are compared without considering the time of hospitalization, this apparently higher incidence of pneumonia in the new series becomes even more pronounced (table 11). The diagnosis of other potentially fatal associated conditions among patients of the new series is described in a footnote to table 13. 4. Approximately 94 per cent of the 151 deaths occurred among the 157 patients who had severe forms of tetanus and 84 per cent among the severely ill patients hospitalized during the first four days of the disease. If all patients with severe tetanus are considered, a difference of 21 per cent in the mortality rates suggests a superiority of the new method of treatment. This difference becomes 25 per cent if the comparison is confined to a consideration of the patients with severe tetanus who were hospitalized during the first four days of the disease. If the patients with moderate and severe forms of tetanus are considered in a single group,[26] the new series shows a mortality rate (45.3 per cent) which is approximately 34 per cent lower than that calculated for the old series (79 per cent). These results,

26. The patients with moderate and severe tetanus are best considered as a single group because the distinction was at times arbitrary and frequently difficult. Furthermore, it appears likely that many of the patients with severe tetanus in the old series would have presented moderately severe clinical pictures if intraspinal therapy had been omitted and effective sedative and general therapy had been employed.

apparently indicating the superiority of the later methods of treatment, are reflected in gross mortality rates which are approximately 30 per cent lower in the new series (35.4 per cent) than in the old (65 per cent).

Study of table 14, which records the general trend of the mortality rates from 1908 to July 1940,[27] discloses five important points. 1. The

TABLE 14.—*The Mortality Among Patients with Tetanus at Cook County Hospital* *

| Period | Intensity of Disease: Mild Recovery | Mild Death | Moderate Recovery | Moderate Death | Severe Recovery | Severe Death | All Intensities Recovery | All Intensities Death | Mortality Percentage | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1908-1913 (Irons, E. E.: J. A. M. A. 44: 1552-1554 [May 8] 1915) | .. | .. | .. | .. | .. | .. | 12 | 41 | 77.3 | |
| 1914 (Irons, E. E.: J. A. M. A. 44: 1552-1554 [May 8] 1915) | .. | .. | .. | .. | .. | .. | 6 | 8 | 57.1 | |
| 1917-1921 (Calvin, J. K., and Goldberg, A. H.: J. A. M. A. 94: 1977-1981 [June 21] 1930) | .. | .. | .. | .. | .. | .. | 19 | 25 | 56.4 | |
| 1922 | 6 | .. | 3 | 2 | 2 | 7 | 11 | 9 | 45.0 | |
| 1925 | 5 | .. | 3 | 2 | .. | 16(1)† | 8 | 18 | 69.2 | 67.3 |
| 1926 | 1 | .. | .. | 2(2) | 1(1) | 5 | 2 | 7 | 77.7 | |
| 1927 | 2 | .. | 1 | .. | .. | 9 | 3 | 9 | 75.0 | |
| 1928 | 4 | .. | 1 | 1 | 1 | 19(1) | 5 | 20 | 80.0 | |
| 1929 | 1 | .. | 3 | .. | .. | 9(2) | 4 | 9 | 69.2 | |
| 1930 | 3 | .. | 1 | 1 | 1 | 10(1) | 5 | 11 | 68.7 | |
| 1931 | .. | .. | 3 | .. | .. | 19 | 3 | 19 | 86.4 | |
| 1932 | 2 | .. | 5 | .. | .. | 4(1) | 7 | 4 | 36.3 | |
| 1933 (to July) | 2 | .. | 3 | .. | .. | 5 | 5 | 5 | 50.0 | |
| 1933 (after July) | 2 | .. | 1 | .. | .. | 2(2) | 3 | 2 | 40.0 | |
| 1934 ‡ | 1 | .. | 6 | 1(1) | 2 | 4(3) | 9 | 5 | 35.7 | |
| 1935 § | 3 | .. | 2 | .. | .. | 6(3)** | 5 | 6 | 54.5§ | |
| 1936 ‡ | 2 | .. | 2 | .. | 5 | 9(5) | 9 | 9 | 50.0 | |
| 1937 | 4 | .. | 3 | .. | 2(1) | 2(2) | 9 | 2 | 18.2 | 35.4 |
| 1938 | 5 | .. | 3(1) | 1†† | 1(1)‡‡ | 5(4)§§ | 9 | 6 | 40.0*** | |
| 1939 | 3 | .. | 7 | .. | 1(1)††† | 4(2)‡‡‡ | 11 | 4 | 26.6 | |
| 1940 (to July) | 1 | .. | 6 | .. | .. | .. | 7 | .. | 0 | |

* The records of patients admitted in 1921 and thereafter have been analyzed in detail and have been considered in table 13 (and the other tables in this report) under the designation "old series."

† The figures in parentheses indicate the number of patients with pneumonia at some time during their stay in the hospital.

‡ A total of 3 patients was treated during 1934 and 1936 with definite departures from the new routine (overzealous sedative therapy, in particular).

§ The tetanus team was not as effectively organized during this period as in preceding and subsequent years. The patients were not centralized, and sedative therapy was unusually intensive in 1935.

** A 41 year old man had retention of nonprotein nitrogen (53.3 mg. urea nitrogen and 3.3 mg. creatinine per hundred cubic centimeters of blood).

†† A 60 year old man had a markedly irregular heart.

‡‡ A 13 year old Negro boy whose pneumonia (upper lobe of left lung) resolved spontaneously and by crisis.

§§ Of those with pneumonia, 1 patient (a 19 year old woman) had septic parotitis and a septic abortion and another (a 59 year old man) had severe stomatitis and other evidences of extreme marked physical neglect preceding hospitalization.

*** If the 3 deaths associated with complications other than pneumonia are excluded, the corrected mortality rate for 1938 is 25 per cent.

††† An 8 year old girl who showed a dramatic response to intravenous injections of sodium sulfapyridine.

‡‡‡ A 6 year old boy had pneumonia and septic parotitis. Neither condition responded to treatment with intravenous injections of sodium sulfapyridine or type-specific antipneumococcus serum.

27. As noted in table 14, the data could not be obtained from the record room for the years 1915, 1916, 1923 and 1924.

gross mortality rate for the period of seven years after July 1933 was 32 per cent lower than that for the preceding period of approximately twenty years, in which the older methods of management were employed. 2. With the former types of treatment, the general trend of the mortality was between 50 and 86.4 per cent. The years 1922 and 1932, however, show unusually low mortality rates. Although the mortality showed marked yearly fluctuations after July 1933, the absence of the exceedingly high peaks previously encountered is significant. Likewise, the unusually low death rates in 1934, 1937, 1939 and 1940 are worthy of attention. Although the results for 1935 appear to be poor, it is to be emphasized that the new routine was not strictly followed during this limited period. The rise in the mortality rate in 1938 was caused by the inclusion of 3 patients who presented conditions which in themselves could have caused death. As noted in a footnote to table 14, omission of these 3 patients yields a corrected mortality rate of 25 per cent for 1938. 3. The main reduction in mortality was among those patients with moderately severe forms of tetanus. 4. The yearly mortality rate for those with severe tetanus reached the lowest level in 1937, when 2 of 4 patients recovered. Otherwise, the fatality rate among those with severe tetanus varied from 64.3 per cent in 1936 to 80 per cent in 1939. 5. The presence of pneumonia and of other complications in the new series influenced the mortality rates in a definite manner. The importance of the proper treatment of these complications has already been discussed in the section on "General Management."

TABLE 15.—*The Relation of the Site of Injury to Mortality*

| Site of Lesion | Series | Number of Patients | Percentage of Patients of Series * | Number of Deaths | Per Cent Mortality |
|---|---|---|---|---|---|
| Upper extremity | Old | 70 | 38.9 | 48 | 68.5 |
| | New | 20 | 20.8 | 6 | 30.0 |
| Lower extremity | Old | 74 | 41.1 | 51 | 68.9 |
| | New | 48 | 50.0 | 17 | 35.4 |
| Head and neck | Old | 7 | 3.9 | 3 | 42.8 |
| | New | 12 | 12.5 | 4 | 33.3 |
| Trunk and external genital organs | Old | 3 | 1.7 | 2 | 66.6 |
| | New | .. | .... | .. | .... |
| Interior of abdomen | Old | 3 | 1.7 | 2 | 66.6 |
| | New | 2 | 2.1 | 1 | 50.0 |
| Unknown or indeterminate | Old | 23 | 12.7 | 11 | 47.8 |
| | New | 14 | 14.5 | 6 | 42.8 |
| All sites | Old | 180 | 100.0 | 117 | 65.0 |
| | New | 96 | 99.9 | 34 | 35.4 |

* The number of patients is divided by the number of patients in the series.

A comparison of the two series of patients in terms of the severity and the site of the local lesion indicated that neither of these factors bore any significant or consistent relation to the mortality rates (tables 9 and 15). The observations recorded in table 15, as well as those reported

elsewhere,[28] are at variance with the belief that the closer the local focus to the central nervous system the greater is the death rate. In this respect, it is of interest that the lowest mortality was encountered among those patients who presented lesions in the region of the head and neck.

The patient's age must be considered in the prognosis. It has been reported [1] that the mortality from tetanus is highest at the extremes of life. For this reason, it is significant that the old and the new series were essentially similar in respect to the percentage distribution of the patients in terms of age group. It is of interest that in the old series the mortality rate was high in all age periods, with the lowest figure among patients 16 to 30 years old and the highest among those over 50 years of age. On the other hand, analysis of the new series revealed no consistent relation between the age of the patient and the mortality rate.

TABLE 16.—*The Relation of Age to Mortality*

| Age Period in Years | Series | Number of Patients | Percentage of Patients * | Number of Deaths | Percentage of Deaths * | Per Cent Mortality |
|---|---|---|---|---|---|---|
| 1 to 15 | Old | 88 | 48.9 | 53 | 45.3 | 60.2 |
| | New | 41 | 42.7 | 13 | 38.2 | 31.8 |
| 16 to 30 | Old | 35 | 19.4 | 17 | 14.5 | 48.6 |
| | New | 17 | 17.7 | 8 | 23.5 | 47.0 |
| 31 to 50 | Old | 41 | 22.8 | 32 | 27.4 | 78.0 |
| | New | 28 | 29.2 | 7 | 20.6 | 25.0 |
| 51 to 78 | Old | 16 | 8.9 | 15 | 12.8 | 93.7 |
| | New | 10 | 10.4 | 6 | 17.6 | 60.0 |
| All age periods | Old | 180 | 100.0 | 117 | 100.0 | 65.0 |
| | New | 96 | 100.0 | 34 | 99.9 | 35.4 |

* The number of patients or the number of deaths is divided by the number of patients in the series.

Nevertheless, it is significant that the highest mortality rate in the new series was noted among the members of the oldest age group.

The temperature of patients with uncomplicated tetanus is usually normal.[1] As indicated in table 12, 177 patients had a record of fever at some time during their stay in the hospital. Approximately 69 per cent of these 177 patients died. In contrast, no deaths occurred (new series) among those whose record indicated a normal temperature (table 12). Tables 11 and 12 describe the importance of pneumonia as a cause of fever, particularly in the new series. Serum therapy was a more important cause of pyrexia in the old series than in the new. This is explained by the fact that repeated injections of tetanus antitoxin (usually intraspinal) were given to patients of the old series. Because of the varied etiologic relations of the fever and because reasons for pyrexia were unknown in one third of the patients of the new series and in approxi-

28. Spaeth, footnotes 1 and 9.

mately two thirds of those in the old, it seems unnecessary to compare the two groups of patients in terms of the incidence of elevated temperature.

## SUMMARY AND CONCLUSIONS

From 1921 to July 1933 patients with tetanus admitted to the Cook County Hospital had been given general ward care, a variety of sedatives and tetanus antitoxin by various technics. About 80 per cent had received serum by the intrathecal route alone or in combination with other channels. In general, repeated doses were injected, so that the averages were approximately 102,000 units for 63 patients who recovered and 58,000 units for 106 who died. In respect to the local lesions, about one half of the entire group of patients had received no treatment, about one-fourth had surgical care and the rest had nonsurgical care. Since July 1933 a new routine has been followed. This has consisted of systematic sedation with avertin with amylene hydrate and sodium amytal (either of the drugs alone or the two in combination), single intravenous and/or intramuscular injections of antitoxin in doses ranging from 20,000 to 100,000 units, the avoidance of any particular emphasis on care of the local lesions and careful general management, with stress on constant nursing care, measures to prevent pneumonia and maintenance of an adequate fluid and caloric intake. One hundred and eighty patients have been treated by the old routine and 96 by the new method.

Comparison of the two series of patients indicates that the incidence of severe forms of tetanus in the old series was about 20 per cent higher than that in the new. The presence of complications, particularly pneumonia, was recognized much more frequently in the new series than in the old.

Approximately 94 per cent of all deaths occurred among those with severe forms of tetanus, and 84 per cent among the severely ill patients hospitalized during the first four days of the disease. The gross mortality rate for the new series (35.4 per cent) was approximately 30 per cent lower than that noted for the old (65 per cent). A significant difference in the mortality rates was demonstrable even when the data were subjected to more rigid methods of statistical analysis. The yearly mortality rates have shown marked fluctuations from 1908 to July 1940, with a well marked tendency toward significantly lower peaks since July 1933. The main reduction in mortality has been among those with moderately severe tetanus. Coexisting diseases and complications influenced the yearly mortality rates.

In uncomplicated tetanus, ordinarily the temperature is normal. About 69 per cent of the patients with fever died, whereas no deaths occurred among those whose temperature remained normal. The cause of the fever was of prognostic significance, as was revealed by the ominous import of pulmonary involvement.

Sedative therapy is the keystone of treatment, and all patients should receive proper sedation. Sodium amytal and avertin with amylene hydrate have proved to be superior to the sedatives previously employed, but the ideal depressant remains to be discovered.

From both the theoretic and the practical point of view, intrathecal serum treatment is to be condemned. Both intraspinal and intracisternal serotherapy are disturbances which apparently increase the intensity of neuromuscular irritability in tetanus.

The intravenous and intramuscular routes, preferably the intramuscular, are recommended for routine use. The technic advised for the administration of antitoxin has been described.

Titration and clinical studies indicate that a single dose of 30,000 units of tetanus antitoxin is satisfactory for active treatment. To allow a liberal margin of safety, a dose of 60,000 units is arbitrarily advised for patients admitted for treatment during the first five days of the disease and one of 40,000 units for mildly to moderately ill patients first treated after the fifth day of disease.

For patients with active tetanus, care of the local lesions is ordinarily not an emergency need and appears to be of relatively minor importance. Amputations and similar measures are warranted only when structures appear to be irreparably destroyed. Treatment of wounds with oxidizing or other solutions may facilitate drainage and may aid the process of healing, but it cannot destroy the tetanus bacilli present locally. The principles of treatment to be followed in the care of wounds in patients with tetanus are identical with those to be recommended in the absence of this disease.

The prompt treatment of complicating pneumonia by present day methods of chemotherapy and serotherapy, in conjunction with customary routine measures, is indicated when this complication supervenes in patients with tetanus.

9030 South Bell Avenue.

# BIOLOGIC FALSE POSITIVE SEROLOGIC REACTIONS IN TESTS FOR SYPHILIS

## II. OCCURRENCE WITH ORGANIC DISEASES OTHER THAN SYPHILIS

CHARLES F. MOHR, M.D.

JOSEPH EARLE MOORE, M.D.

AND

HARRY EAGLE, M.D.

BALTIMORE

Many infectious diseases have been reported as causing biologic false positive serologic reactions for syphilis. That some of them (malaria, leprosy and infectious mononucleosis) cause such reactions has been well established. Other diseases, e. g., relapsing fever, rat bite fever, scarlet fever, tuberculosis, pneumonia, Vincent's infections, malignant conditions (particularly cancer of the tongue), subacute bacterial endocarditis, glanders, Weil's disease, leishmaniasis, lymphogranuloma venereum, trypanosomiasis, typhus fever, vaccinia and infections of the upper respiratory tract, as well as injections of horse serum, have from time to time been suggested as causing such serologic reactions, but the evidence is as yet inconclusive.

From a review of the literature it is impossible to arrive at any conclusions regarding the percentage of biologic false positive reactions obtained in any of these diseases except leprosy and infectious mononucleosis. Until recently it was thought that biologic false positive reactions were obtained in only 10 to 15 per cent of patients with malaria. When this disease was carefully studied by means of serially repeated tests, first by Ester [1] and later by Kitchen, Webb and Kupper,[2] it was found by them that 90 to 100 per cent of malarial patients at some time in the course of the disease had biologic false positive serologic reactions for syphilis. These observations strongly suggest that, particularly in infectious diseases, the incidence of false positive reactions cannot be

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital, and the United States Public Health Service.

1. Ester, F.: Sul comportamento di alcune sieroreazione della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, Gior. di batteriol. e immunol. **17**:502 (Oct.) 1936.

2. Kitchen, S. F.; Webb, E. L., and Kupper, W. H.: The Influence of Malarial Infection on the Wassermann and Kahn Reactions, J. A. M. A. **112**:1443 (April 15) 1939.

determined by single specimens of serum. Serial specimens, taken daily if possible, should be studied, as the false positive reactions may occur on only one or two days.

To illustrate the type of serologic response associated with infectious diseases, we have selected for report 11 cases in which biologic false positive serologic reactions for syphilis were associated with infections other than syphilis.

## REPORT OF CASES

CASE 1.—A white man aged 26, a physician, had a serologic test for syphilis in November 1938, because he wished to act as a donor for a transfusion. The result of this test was reported as positive. Reactions in serologic tests for syphilis performed on several occasions during the two years prior to this test had always been negative. There was no history of sexual exposure or of accidental infection with Spirochaeta pallida. About one week after the positive reaction was reported, low grade fever developed, with a daily temperature ranging from 99 to 99.8 F. There were no symptoms other than malaise, fatigue and, at times, excessive perspiration. Physical examination disclosed nothing abnormal except one palpable left posterior auricular node, a few shotty nodes in the posterior cervical triangles and a few small nodes in the left axilla. The edge of the spleen was definitely palpable. Routine laboratory studies yielded data as follows: The red blood cell count was 4,670,000; the hemoglobin concentration, 91 per cent; the white blood cell count, 7,850, and the differential count, 64 per cent neutrophils, 31 per cent lymphocytes, 4.5 per cent monocytes, and 0.5 per cent basophils. The red and white blood cells were apparently normal. No malarial parasites were seen in the blood smear. The urine and stool were normal. A test for heterophil antibody gave negative results. The agglutination test for typhoid H was positive in a dilution of 1 : 160 and doubtful in dilutions to 1 : 1,250. The agglutination test for typhoid O was negative. Agglutination tests for Bacillus abortus, Salmonella suipestifer and paratyphoid A and B bacilli were all negative. The cerebrospinal fluid showed no abnormal changes.

In June 1939 the patient married. In spite of the fact that he has received no antisyphilitic treatment and that no prophylactic precautions have been taken in sexual relations, his wife remains free from syphilis (May 1940).

In August 1939, while in another city, the patient had an acute attack of abdominal pain, with boardlike rigidity of the abdomen. His temperature was 99 F. The white blood cell count was 14,500, with 90 per cent neutrophils. It was thought that possibly he had a perforated gastric ulcer or acute pancreatitis. A laparotomy was performed, but nothing could be found except an enlarged spleen. He made an uneventful recovery and has had no recurrence of the abdominal pain. Unfortunately, no serologic test for syphilis was done during this episode.

In January 1940 he was reexamined; he was asymptomatic, and nothing abnormal was found on physical examination. Laboratory studies gave information as follows: The red blood cell count was 4,820,000, and the white blood cell count, 9,400 with a normal differential count. The agglutination test for typhoid H was reported as weakly positive in a dilution of 1 : 80. The agglutination test for typhoid O was negative. The serologic tests for syphilis are summarized in table 1.

The exact nature of this patient's infection is unknown. In November 1938, several weeks after the onset of his first illness, he was still suffer-

ing from malaise and fatigue and had a palpable spleen. At that time it was our impression that he might have either infectious mononucleosis or brucellosis, though neither of these diseases could have been responsible for the acute abdominal pain which developed eleven months later. This may have been an entirely different infection, but in view of the fact that the patient still had an enlarged spleen at the time of operation and has persistently had a slight elevation of the white blood cell count, it is reasonable to believe that the two episodes were related and that the patient was suffering from an infection of unknown cause and that this involvement has now subsided. Concurrently, the serologic tests for

TABLE 1.—*Serologic Tests for Syphilis, Case 1* *

| Date | Laboratory | Wassermann | Kahn Standard | Eagle Microflocculation | Eagle Macroflocculation | Kline Diagnostic | Hinton | Laughlen | Spirochetal (Pallida) | Clinical Findings |
|---|---|---|---|---|---|---|---|---|---|---|
| 9/37 | 1 | .. | .. | 0 | .. | .. | .. | .. | .. | Normal |
| 7/38 | 1 | .. | .. | 0 | .. | .. | .. | .. | .. | |
| 11/ 1/38 | 2 | P | D | .. | .. | .. | .. | D | .. | Normal |
| 11/ 3/38 | 2 | P | D | .. | .. | .. | .. | D | .. | |
| 11/17/38 | 2 | P | D | .. | .. | .. | .. | .. | .. | Fever, malaise and fatigue, beginning Nov. 6 |
| 11/18/38 | 2 | .. | 0 | .. | .. | .. | .. | D | .. | |
| 11/22/38 | 1 | 0 | .. | 0 | .. | .. | .. | .. | .. | Malaise, fatigue, adenopathy and enlarged spleen |
| 11/26/38 | 3 | 0 | 0 | .. | 0 | .. | .. | .. | .. | |
| | 4 | 0 | P (1 unit) | 0 | .. | P (3 units) | 0 | .. | .. | |
| 2/28/39 | 4 | D | D | 0 | .. | P (1 unit) | 0 | .. | 0 | Good health, except for acute abdominal pain Aug. 24, 1939 |
| 3/15/39 | 3 | 0 | 0 | .. | 0 | .. | .. | .. | .. | |
| 8/15/39 | 4 | 0 | 0 | 0 | .. | D | 0 | .. | .. | |
| 1/31/40 | 3 | 0 | 0 | .. | 0 | .. | .. | .. | 0 | |

* In this table and in subsequent tables, laboratories are designated as 1, 2, 3, etc. Results of serologic tests are expressed as positive (P), doubtful (D), negative (0) and anticomplementary (A. C.). If a quantitative titration in a positive test was performed, the titer, expressed in units of reagin (serum dilution), is parenthetically inserted after the positive result.

syphilis, which gave only weakly positive reactions and which were marked by conflicting results from different laboratories and with different technics, have spontaneously given negative reactions and have continued to do so for nearly a year.

CASE 2.—A white man aged 24, a physician, acted as a blood donor on numerous occasions during the four years he was in medical school. Results of serologic tests for syphilis, done before each transfusion, were always negative. He was examined here on Oct. 27, 1938. Five weeks prior to this examination he had had a head cold and slight cough, which were followed in a few days by an abrupt onset of deafness and tinnitus in the left ear. Within twenty-four hours after the onset of these symptoms, vertigo developed, with nausea and nystagmus. The temperature at the onset of this illness was 98.6 F. Three weeks after the onset of symptoms, serologic reactions for syphilis were found to be positive. There was no history of either acquired or congenital syphilitic infection. The physical

examination showed no abnormal condition except in the ears. Complete audiographic studies were made. There was marked bilateral loss of hearing, more striking on the left side. Air conduction was greater than bone conduction on both sides, and vibration sense in Weber's test was referred to the right. At the time of examination, on October 25, the vertigo had disappeared but the loss of hearing had progressed. Otherwise the patient felt well. The results of routine laboratory studies were without significance. Examination of the cerebrospinal fluid revealed nothing abnormal. On reexamination by the otolaryngologist in June 1939, it was noted that the patient still had tinnitus in the left ear but that hearing in both ears had returned to normal. A summary of the serologic findings is outlined in table 2. No antisyphilitic treatment was given at any time.

Labyrinthitis, of unknown cause, developed in September 1938. Apparently during its course reagin appeared in the patient's blood. The

TABLE 2.—*Serologic Tests for Syphilis, Case 2*

| Date | Laboratory | Wassermann | Kahn Standard | Eagle Microflocculation | Eagle Macroflocculation | Kline Diagnostic | Hinton | Kline Exclusion | Clinical Findings |
|---|---|---|---|---|---|---|---|---|---|
| 10/11/38 | 1 | 0 | P | .. | .. | P | .. | P | Slight vertigo and tinnitus; moderate loss of hearing; no fever |
| | 2 | 0 | .. | P | .. | .. | .. | .. | |
| 10/21/38 | 3 | .. | 0 | .. | .. | D | .. | P | |
| | 3 | 0 | .. | .. | .. | 0 | .. | 0 | |
| 10/25/38 | 1 | 0 | D | 0 | .. | D | .. | P | No tinnitus or vertigo; moderate loss of hearing; no fever |
| | 2 | 0 | .. | 0 | .. | .. | .. | .. | |
| 10/27/38 | 3 | .. | .. | .. | .. | D | .. | P | |
| | 5 | .. | D | .. | .. | .. | 0 | P | |
| | 6 | 0 | 0 | .. | 0 | .. | .. | .. | |
| 11/ 4/38 | 7 | 0 | 1 & 1:10 0 0 | 1 & 1:10 0 0 | .. | 1 & 1:10 P 0 | 0 | .. | |
| | 7 | 0 | 0 | 0 | .. | 0 | 0 | .. | |
| 4/14/39 | 7 | 0 | 0 | 0 | .. | 0 | 0 | .. | Well; occasional tinnitus; normal hearing |

results of serologic tests for syphilis spontaneously reversed to negative within three weeks and have remained so for six months.

CASE 3.—A white man aged 33, an economist, presented himself to his family physician for a routine physical examination. A serologic test done at the time gave a positive reaction. Two weeks before this examination the patient had been vaccinated against smallpox. Twenty-four hours after vaccination he had a fever lasting one day; the fever returned after several days and then lasted about four days. The temperature was at times as high as 103 F. For the next few weeks the patient felt weak and had frequent gastrointestinal upsets. At the time he was examined by his physician the vaccination scar had not healed. The patient gave no history of primary or secondary syphilis. Four to five years previously he had a sore throat which was diagnosed as Vincent's infection, but this was not associated with symptoms suggesting the early stages of syphilis. The lesion in the throat disappeared in one week with local treatment. One year ago the patient was told that he had an ulcerative lesion of the nasal septum; it lasted about six weeks, in spite of local treatment. About four years ago he had gonococcic urethritis, complicated by epididymitis. The onset of gonorrhea followed

his only extramarital sexual exposure. The patient has been married for six years, and his wife has negative serologic reactions for syphilis. Physical examination showed nothing abnormal except epidermophytosis of the feet, an unhealed vaccination wound (dark field examination of serum expressed from this yielded nothing significant) and slight induration of the right epididymis. All routine laboratory tests, with the exception of the serologic tests for syphilis, revealed nothing significant. An occasional red blood cell was seen in one specimen of urine. The urine was entirely normal on repeated examinations. A test for heterophil antibody gave negative results. The cerebrospinal fluid was normal. The serologic tests are summarized in table 3.

This patient had a marked local and constitutional reaction to smallpox vaccine. Because the reactions to serologic tests for syphilis were positive during the time the vaccination reaction persisted and became

TABLE 3.—*Serologic Tests for Syphilis, Case 3*

| Date | Laboratory | Wassermann | Kahn Standard | Eagle Microflocculation | Eagle Macroflocculation | Clinical Findings |
|---|---|---|---|---|---|---|
| 8/ 1/38 | 1 | P | P | .. | .. | Malaise; vaccination wound from inoculation July 15; no fever |
| 8/13/38 | 2 | P (2.5 units) | P | .. | P | Vaccination wound not healed |
| 8/15/38 | 2 | P (2.5 units) | P | .. | P | |
| 8/17/38 | 3 | D | P | .. | .. | |
| 8/25/38 | 2 | 0 | 0 | .. | 0 | |
| 8/26/38 | 4 | P (4 units) | .. | P | .. | Vaccination wound healed; well |
| 9/ 7/38 | 2 | 0 | 0 | .. | P | |
| 9/14/38 | 2 | 0 | 0 | .. | P | |
| 9/21/38 | 2 | 0 | 0 | .. | 0 | Well |
| 9/23/38 | 2 | 0 | 0 | .. | 0 | |
| 11/ 9/38 | 2 | 0 | 0 | .. | 0 | |

negative shortly after the constitutional and local reaction had subsided, we believe vaccinia to be responsible for these false positive serologic reactions for syphilis. This is the second case reported in the literature in which such a response occurred.

Barnard [3] reported the first case in which a biologic false positive serologic reaction for syphilis was caused by vaccinia. The patient was a white student 24 years of age who had had repeatedly negative serologic reactions before he was vaccinated, the last negative response being obtained six months before vaccination. A routine serologic test done during the period when the local vaccination lesion was present gave a positive response. The serologic reactions reverted to negative after

3. Barnard, R. D.: False Positive Serologic Tests for Syphilis Following Vaccination for Variola, Illinois M. J. **77**:78 (Jan.) 1940.

four weeks and remained negative when repeated during the following four months. Giordano [4] has observed, but not reported, a similar case.[4a]

CASE 4.—A white man aged 24, a store manager, was admitted to the hospital on Oct. 23, 1937 with bronchopneumonia. For two weeks prior to his admission he had had fever, the temperature occasionally reaching 102 F. He had been suffering from generalized aches and pains and had had a cough for about one week prior to admission. There was no history of acquired or congenital syphilis. On his admission to the hospital, the physical examination showed nothing abnormal except physical signs of consolidation in the left lung. Roentgenologic examination of the chest at this time revealed infiltration of small areas in the upper and middle lobes of the right lung and the upper lobe of the left lung. The routine laboratory studies yielded data as follows: The white blood cell count was 16,200, and the differential count, 12 per cent juvenile neutrophils, 77 per cent neutrophils, no eosinophils, no basophils, 8 per cent lymphocytes and 3 per cent monocytes. Pneumococci could not be typed from the sputum. The blood culture showed no growth. The urine and stool were normal. The level of blood non-

TABLE 4.—*Serologic Tests for Syphilis, Case 4*

| Date | Laboratory | Wassermann | Kahn Standard | Eagle | Hinton | Kline Diagnostic | Clinical Findings |
|---|---|---|---|---|---|---|---|
| 10/28/37 | 1 | P | .. | D | .. | .. | Fever; roentgenographic evidence |
| 11/ 2/37 | 1 | P | .. | D | .. | .. | of bronchopneumonia |
| 11/ 7/37 | 1 | .. | .. | 0 | .. | .. | No fever; resolution |
| 11/10/37 | 1 | .. | .. | 0 | .. | .. | No fever; convalescence |
| 12/ 5/37 | 2 | .. | 0 | .. | .. | 0 | Well |
| 1/12/38 | 2 | .. | 0 | .. | .. | 0 | |
| 2/20/38 | 2 | .. | 0 | .. | .. | 0 | |
| 3/15/39 | 3 | 0 | 0 | 0 | 0 | 0 | |

protein nitrogen was 40 mg. per hundred cubic centimeters; the level of blood sugar, 81 mg. per hundred cubic centimeters, and the carbon dioxide-combining power, 60 volumes per cent. The level of chlorides was 90.8 milliequivalents per hundred cubic centimeters. The test for heterophil antibody gave a negative result. The serologic tests for syphilis are summarized in table 4.

CASE 5.—A single white woman aged 25, a nurse, had a chill and pain in the chest and began to cough on May 7, 1938. She was admitted to the hospital two days later and on admission was found to have bronchopneumonia. Pulmonary infiltration was confined to the upper lobe of the right lung. From May 9 to May 15 the temperature ranged from 99 to 102 F. On her admission the white blood cell count was 6,650; the red cell count, 4,890,000, and the hemoglobin concentration, 98 per cent. Pneumococci could not be typed from the sputum; a

4. Giordano, A. S.: Personal communication to the authors.

4a. Since the preparation of this paper false positive serologic reactions for syphilis have been reported in a high proportion of patients with vaccinia by Thomas and Garrity (Routine Kahn Blood Reactions, U. S. Nav. M. Bull. **39**:272 [April] 1941) and by Lynch, Boynton and Kimball (False Positive Serologic Reactions for Syphilis, J. A. M. A. **117**:591 [Aug. 23] 1941).

culture of the sputum contained 20 per cent pneumococci, 20 per cent Staphylococcus albus and 60 per cent Staphylococcus aureus. Culture of the sputum and guinea pig inoculations of the sputum were negative for tubercle bacilli. Blood cultures showed no growth. On admission, the Eagle flocculation test gave a negative result. Six days after admission, however, the patient was transferred to another ward, where the flocculation test was routinely repeated and the result found to be positive. The patient gave no history of syphilis, nor could any evidence of syphilis be found on physical examination. Results of repeated

TABLE 5.—*Serologic Tests for Syphilis, Case 5*

| Date | Laboratory | Wassermann | Kahn Standard | Eagle Macroflocculation | Eagle Microflocculation | Hinton | Kline Diagnostic | Spirochetal (Pallida) | Clinical Findings |
|---|---|---|---|---|---|---|---|---|---|
| 5/11/38 | 1 | .. | .. | .. | 0 | .. | .. | .. | Fever; partial consolidation of upper lobe of right lung |
| 5/17/38 | 1 | P | .. | .. | P | .. | .. | .. | Fever; consolidation of upper lobe of right lung |
| 5/28/38 | 2 | P (100 units) | P | P | .. | .. | .. | .. | Convalescence; no fever; no clinical evidence of consolidation |
| 5/31/38 | 2 | P (40 units) | P | P | .. | .. | .. | .. | Discharge from hospital; no fever |
| 6/ 1/38 | 2 | P (40 units) | P | P | .. | .. | .. | .. | Well |
| 6/ 3/38 | 2 | P (13.3 units) | P | P | .. | .. | .. | .. | |
| 6/ 7/38 | 2 | P (13.3 units) | P | P | .. | .. | .. | .. | |
| 6/ 9/38 | 2 | P (13.3 units) | P | P | .. | .. | .. | .. | |
| 6/13/38 | 3 | P (22 units) | .. | .. | P | .. | .. | 0 | |
| | 2 | P (5 units) | P | P | .. | .. | .. | .. | |
| 6/14/38 | 2 | P (1 unit) | P | D | .. | .. | .. | .. | |
| 6/16/38 | 2 | P (1 unit) | P | D | .. | .. | .. | .. | |
| 6/28/38 | 4 | D | .. | .. | P | .. | .. | .. | |
| 7/ 6/38 | 4 | .. | .. | .. | 0 | .. | .. | .. | |
| 7/12/38 | 4 | D | .. | .. | 0 | .. | .. | .. | |
| 7/19/38 | 4 | D | .. | .. | 0 | .. | .. | .. | |
| 7/25/38 | 4 | D | .. | .. | 0 | .. | .. | .. | |
| 8/23/38 | 2 | 0 | .. | .. | 0 | .. | .. | .. | |
| 2/24/39 | 3 | 0 | 0 | .. | 0 | 0 | 0 | .. | |
| 3/ 1/39 | 1 | 0 | .. | .. | 0 | .. | .. | .. | |
| | 2 | 0 | 0 | 0 | .. | .. | .. | .. | |
| | 3 | 0 | 0 | .. | 0 | .. | 0 | .. | |

serologic tests in the five years preceding this admission had all been negative. She admitted sexual exposure with one man only, her fiancé. The man was examined and found to be free from all evidence of syphilis. The patient was afebrile, and the consolidation of the lung had entirely cleared by May 23. A summary of the serologic tests on this patient is given in table 5.

CASE 6.—A white woman aged 40, a housewife, was first admitted to the hospital in 1927, complaining of arthritis of the hands and shoulders. At this time her tonsils and adenoids were removed. No serologic test for syphilis was done. The patient returned to the hospital in 1928, with the new complaints of abdominal pain, nausea, vomiting and diarrhea. She remained in the hospital for only

twenty-four hours, but the routine history and physical examination showed nothing abnormal. Again, no serologic tests for syphilis were done. She was again admitted to the hospital in 1934, because of chronic infectious arthritis of the right thumb. With the exception of the right thumb, which was somewhat swollen and painful on active and passive motion, her physical examination showed nothing abnormal. Results of the serologic tests for syphilis, performed for the first time, were negative.

On Feb. 24, 1935 the patient was again admitted to the hospital, this time because of lobar pneumonia. She had been sick for eight days preceding this admission with what was thought to be grip. The temperature had been ranging from 102 to 103 F. On admission her temperature was 104 F. Physical examination showed signs of lobar pneumonia. Roentgenologic examination of the chest confirmed these findings. Aside from the findings in the chest, the results of the physical examination were entirely normal. She gave no history of syphilitic infection. Type IV pneumococci were found in the sputum. A blood culture yielded no growth. The blood counts were as follows: red cells, 4,120,000; white cells, 20,500, and differential count, 92 per cent neutrophils, no eosinophils, 4 per cent lymphocytes and 4 per cent monocytes. The urine and stool were both

TABLE 6.—*Serologic Tests for Syphilis, Case 6*

| Date | Laboratory | Wassermann | Standard | Eagle Macroflocculation | Eagle Microflocculation | Kline Diagnostic | Clinical Findings |
|---|---|---|---|---|---|---|---|
| 6/34 | 1 | 0 | .. | 0 | .. | .. | Chronic infectious arthritis |
| 2/24/35 | 1 | P | .. | P | .. | .. | Fever; lobar pneumonia |
| 2/27/35 | 1 | P | .. | P | .. | .. | |
| 1/27/37 | 1 | 0 | .. | .. | 0 | .. | Well |
| | 2 | 0 | 0 | 0 | .. | .. | |
| 12/27/39 | 1 | .. | .. | .. | 0 | 0 | Fever; bronchitis; pharyngitis |

normal. Routine serologic tests for syphilis were done; the results of the Eagle flocculation test and the Wassermann test were positive. The patient made an uneventful recovery and was discharged.

Although many attempts were made to have her return for serologic examinations, the patient refused to have further tests done until January 1937. Meanwhile, her husband was found to be free from all evidences of syphilis.

The patient was again admitted to the hospital on Dec. 27, 1939, complaining of a head cold and cough of two days' duration. The temperature was 100 F. Nothing could be found on physical examination. The diagnosis was acute bronchitis and pharyngitis. Serologic tests were done at this time, and reactions to the Eagle flocculation and Kline tests were negative. A summary of the serologic tests on the patient is given in table 6.

CASE 7.—A male Negro child aged 15 months was examined in the pediatric clinic on May 23, 1939, when he was found to have marked anemia, bilateral otitis media, rhinopharyngitis and meningismus. There were no lesions or history suggestive of congenital syphilis, and serologic reactions of both the blood and the cerebrospinal fluid were negative for syphilis. The hemoglobin concentration was 30 per cent. The child was admitted to another hospital for treatment. While

at this hospital he received a transfusion because of anemia. The donor for this transfusion had been thoroughly examined and found to be nonsyphilitic. After a lapse of about six weeks, on July 3, 1939, the child returned to the pediatric dispensary with cough and bilateral otitis media still present. Serologic tests for syphilis were repeated and the results reported as positive. Roentgenograms of the long bones were normal, and a roentgenogram of the chest was unsatisfactory.

Physical examination at this time showed nothing significant except otitis media. The child was followed at frequent intervals in the dispensary from July 3 to July 27; during this period his temperature fluctated between 98.8 and 101.4 F. On July 27 roentgenologic examination of the chest revealed bronchopneumonia of the right lung. The child was admitted to the ward. At this time he was also found to have physical signs of pneumonia of the right lung. His white blood cell count was 27,000, with 89 per cent neutrophils. The hemoglobin concentration on admission was 59 per cent. The child recovered from pneumonia

TABLE 7.—*Serologic Tests for Syphilis, Case 7*

| Date | Laboratory | Wassermann | Eagle Microflocculation | Kline Diagnostic | Kline Exclusion | Clinical Findings |
|---|---|---|---|---|---|---|
| 5/27/39 | 1 | .. | .. | .. | 0 | Anemia; otitis media; slight fever |
| 7/ 5/39 | 2 | A. C. | P | .. | .. | Otitis media; slight fever; cough |
| 7/ 7/39 | 2 | A. C | P | .. | .. | |
| 7/17/39 | 2 | 0 | D | .. | .. | Fever; bronchopneumonia |
| 7/25/39 | 2 | 0 | D | .. | .. | |
| 8/ 2/39 | 2 | 0 | D | .. | .. | No fever; lungs clearing |
| 9/ 5/39 | 2 | 0 | D | .. | .. | Fever; nasopharyngitis |
| 11/ 1/39 | 2 | 0 | 0 | .. | .. | Well |
| 1/ 9/40 | 2 | 0 | 0 | .. | .. | |
| 2/ 7/40 | 2 | 0 | 0 | .. | .. | Slight fever; cervical adenitis |
| 4/ 3/40 | 2 | 0 | 0 | .. | .. | Well |
| 6/ 5/40 | 2 | .. | 0 | .. | .. | |

and was discharged on August 13. He remained well until September 5, when he again had a temperature of 100 F. Nothing could be found to explain the fever except nasopharyngitis. His white blood cell count was 19,400, with 80 per cent neutrophils. The hemoglobin concentration by this time had increased to 82 per cent. The child was well in two days and was discharged. His mother has been examined and gives no history or physical signs of syphilis; her reactions to serologic tests for syphilis are negative. The serologic tests in this case are summarized in table 7.

Unfortunately, serologic tests for syphilis had not been done in case 4 prior to the patient's admission to the hospital with pneumonia. Two or more negative serologic reactions had been obtained in cases 5 and 6 and one in case 7 prior to the patients' admissions with pneumonia. The serologic reactions reverted to negative in all 4 cases after recovery from the acute disease—in case 4 in three days, in case 5 in two months and

in case 7 in one month after the temperature became normal. The interval between recovery from pneumonia and reversion of the serologic reactions for syphilis to negative is unknown in case 6.

Only 1 of these 4 patients had pneumococcic pneumonia; the etiologic agent in the cases of the other 3 patients is not known. None received serum therapy, an important point inasmuch as injections of horse serum have been reported to produce biologic false positive reactions.[5]

Reports of biologic false positive serologic reactions for syphilis associated with pneumonia are few. Eldh [6] did serologic tests on 20,798 medical patients and found that 52 had presumably biologic false positive reactions. Twenty-six of these 52 patients had pulmonary disease, of whom 10 had pneumonia, 6 emphysema, 7 tuberculosis and 3 influenza with bronchitis. Krag and Lønberg [7] had a similar experience. In testing the serums of 120,000 presumably nonsyphilitic patients they found that 53 patients had biologic false positive serologic reactions for syphilis, so far as they presented no clinical evidence or history of syphilis infection. Sixty per cent of them [8] had infections of the respiratory tract, and 13 per cent [5b] had pneumonia. Boas and Neergaard [9] reported the cases of 1 patient with bronchopneumonia and 2 with bronchitis whose serums gave biologic false positive reactions. Kissmeyer [10] reported 10 cases, in which the patients had biologic false positive serologic reactions for syphilis. In 2 of these cases the diagnosis of pneu-

5. (*a*) Hentschel, H., and Szego, L.: Neue Serumbefunde an Diphtherie-Rekonvaleszenten, Klin. Wchnschr. **8**:1395 (July 23) 1929. (*b*) Wichels, P.; Hürthle, R., and Maley: Ein Beitrag zur Theorie und Praxis der Syphilisreaktionen, München. med. Wchnschr. **76**:1759 (Oct. 18) 1929. (*c*) Frei, W.: Serologische Untersuchungen nach Pferdeseruminjektionen, nach Pferdefleisch-sowie nach Ziegenmilchernährung, Klin. Wchnschr. **8**:2134 (Nov. 12) 1929. (*d*) Boas, H., and Tølbøll, G.: Kann eine Injektion von Diphtherieserum eine positive Seroreaktion auf Syphilis bei einem Nicht-Syphilitiker hervorrufen? Dermat. Wchnschr. **94**:173 (Jan. 30) 1932. (*e*) Stern, C.: Positive Seroreaktion auf Syphilis nach Infektion von Diphtherieserum, München. med. Wchnschr. **79**:583 (April 8) 1932.

6. Eldh, S. M.: Specificity of the Wassermann Reaction in Almost 21,000 Nonsurgical Cases, Svenska läk.-tidning. **29**:373 (April 8) 1932.

7. Krag, P., and Lønberg, A.: The Occurrence of Strong Non-Specific Wassermann-Kahn Reactions, Acta dermat.-venereol. **19**:612 (Dec.) 1938.

8. Edelman, S. D., and Haber, G. B.: Rat-Bite Fever: Report of Three Cases with Review of the Literature, J. Pediat. **5**:520 (Oct.) 1934.

9. Boas, H., and Neergaard, I. S.: Kommt eine positive Wassermann-Reaktion gelegentlich bei febrilen Lungenaffectionen vor? Dermat. Ztschr. **71**:6 (March) 1935.

10. Kissmeyer, A.: Some Views on the Interpretation and Evaluation of the "Nonspecific" Seroreaction in Syphilis, Ugesk. f. læger **99**:213 (Feb. 25) 1937.

monia was made. Stryjecki [11] stated that about 5 per cent of patients with pneumonia have biologic false positive serologic reactions for syphilis.

CASE 8.—A single white woman aged 19, a nurse, began to complain of malaise, generalized aching and sore throat about March 1, 1935. Twenty-four hours after these first symptoms appeared slight fever developed. About forty-eight hours after the onset of fever a generalized macular eruption appeared over the face and trunk. This rash persisted for about thirty-six hours. The temperature fell to normal when the rash disappeared. The patient said there had been no sexual exposure or recent kissing. No lesions had been present in the past which might suggest an extragenital chancre. The patient had no signs or symptoms of congenital syphilis. The patient's mother and father are living and well. The mother had one miscarriage after the birth of the patient.

TABLE 8.—*Serologic Tests for Syphilis, Case 8*

| Date | Laboratory | Wassermann | Kahn Standard | Eagle Macroflocculation | Eagle Microflocculation | Kline Diagnostic | Clinical Findings |
|---|---|---|---|---|---|---|---|
| 3/ 5/35 | 1 | D | P | .. | .. | .. | Fever; macular rash |
| 3/ 7/35 | 1 | P | P | .. | .. | .. | Malaise; fatigue |
| | 2 | P (16 units) | P | .. | .. | .. | |
| 3/15/35 | 2 | P (10 units) | D | .. | .. | .. | |
| | 3 | 0 | .. | .. | .. | .. | |
| | 4 | P | .. | .. | .. | .. | |
| | 5 | 0 | 0 | .. | .. | .. | |
| 6/ 3/35 | 1 | 0 | 0 | 0 | .. | .. | Well |
| 9/10/35 | 1 | 0 | 0 | .. | .. | .. | |
| 12/ 3/36 | 1 | 0 | 0 | .. | .. | .. | |
| 3/ 4/40 | 2 | .. | .. | .. | 0 | 0 | |
| | 6 | 0 | 0 | .. | .. | .. | |

Physical examination on March 15, 1935, two weeks after the acute illness, gave entirely normal results. There was no generalized enlargement of lymph nodes; the spleen was not palpable, and the hymen was intact. At the time of the first symptoms the white blood cell count was 8,600, and the differential count revealed 62 per cent neutrophils, 4 per cent eosinophils, 30 per cent lymphocytes and 4 per cent monocytes. The test for heterophil antibody was not done at the time the patient gave positive serologic reactions for syphilis; however, one several weeks later gave a negative result. The serologic tests are summarized in table 8.

CASE 9.—A single white woman aged 19, a student, applied for admission to an out-of-town nurses' training school on Aug. 5, 1939. Her routine physical examination showed nothing significant, but the routine serologic tests for syphilis gave positive results. She gave no history of a syphilitic infection, nor had she had any sexual exposures. Two weeks before her first serologic tests were done she had a sore throat, which lasted about three days. She consulted her family physician, who noted a white patch on the left tonsil but no enlargement of the lymph node. She does not think she had fever at this time.

11. Stryjecki, T.: Ueber die positive unspezifische und vorübergehende Wassermann- Reaktion, Wien. klin. Wchnschr. **51**:1131 (Oct. 14) 1938.

She was examined here on September 20, at which time she was completely asymptomatic. Results of the physical examination showed nothing abnormal, and the hymen was intact. The temperature was 99.2 F. The red blood cell count was 4,980,000; the white blood cell count was 11,950, and the differential count revealed 65 per cent neutrophils, 2 per cent eosinophils, 20 per cent lymphocytes, 12 per cent monocytes and 1 per cent myelocytes. The sedimentation rate was 4 mm. in one hour. The urine was normal. The test for heterophil antibody gave a negative result. The reactions to serologic tests done on her mother and father were negative. The serologic tests on the patient are summarized in table 9.

TABLE 9.—*Serologic Tests for Syphilis, Case 9*

| Date | Laboratory | Wassermann | Kahn Standard | Eagle Macroflocculation | Eagle Microflocculation | Clinical Findings |
|---|---|---|---|---|---|---|
| 7/23/39 | .. | .. | .. | .. | .. | Sore throat; no fever? |
| 8/ 5/39 | 1 | P | 0 | .. | .. | Well |
| 9/ 7/39 | 2 | 0 | 0 | .. | .. | |
| | 1 | P | 0 | .. | .. | |
| | 3 | P | 0 | .. | .. | |
| 10/20/39 | 4 | P | 0 | .. | .. | |
| | 5 | P (7.5 units) | 0 | D | .. | |
| | 5 | 0 | 0 | 0 | .. | |
| 4/ 4/40 | 6 | 0 | .. | .. | 0 | |
| | 5 | 0 | 0 | 0 | .. | |

TABLE 10.—*Serologic Tests for Syphilis, Case 10*

| Date | Laboratory | Wassermann | Eagle Microflocculation | Spirochetal (Pallida) | Clinical Findings |
|---|---|---|---|---|---|
| 4/17/39 | 1 | .. | 0 | .. | Sore throat; fever; test for heterophil antibodies positive 1:128 |
| | 2 | P | 0 | 0 | |
| 4/24/39 | 2 | 0 | 0 | .. | |

CASE 10.—A single white woman aged 25, a student, was admitted to the hospital on April 17, 1939, because of a sore throat and a temperature of 101.4 F. There was no history of syphilitic infection. Physical examination showed nothing significant except a red pharynx, with grayish exudate in both tonsillar fossae. A few moist rales were heard at the base of the left lung, but the roentgenogram of the chest was reported as normal. Laboratory examinations on April 17, 1939, yielded data as follows: A smear from the exudate in the tonsillar fossae showed many Vincent's organisms. The red blood cell count was 4,050,000; the hemoglobin content, 15 Gm. per hundred cubic centimeters; the white cell count, 9,840, and the differential count, 9 per cent juvenile neutrophils, 41 per cent neutrophils, no eosinophils, 1 per cent basophils, 6 per cent monocytes and 43 per cent lymphocytes. The test for heterophil antibody gave a positive reaction in a dilution of 1:128. The Wassermann reaction was positive, and the result of the Eagle flocculation test was negative. On April 24, 1939 the test for heterophil antibody was

repeated, and again the result was positive in a dilution of 1:128. The white blood cell count on this date was 7,400, and the differential count, 4 per cent juvenile neutrophils, 21 per cent neutrophils, no eosinophils, no basophils, 8 per cent monocytes and 67 per cent lymphocytes. Many lymphocytes typical of the cells occurring in cases of infectious mononucleosis were seen in the smear. The serologic tests are summarized in table 10.

Cases 8, 9 and 10 had one factor in common, sore throat. Unfortunately, the patients in cases 8 and 9 were not seen by us at the time of the acute infection, nor did they have tests for heterophil antibody done at that time. Both of them may have had some type of sore throat other than that associated with infectious mononucleosis. Case 10 was undoubtedly one of infectious mononucleosis. The test for heterophil antibody gave a positive result in a dilution of 1:128, and the blood smear was typical for that disease.

From a review of the cases reported in the literature it is apparent that no particular cause of sore throat is associated with biologic false positive serologic reactions for syphilis. At least 14 cases of biologic false positive serologic reactions for syphilis associated with scarlet fever have been reported. In 1 of Kissmeyer's [10] 10 cases, in 3 of Krag and Lønberg's [7] 53 cases and in 5 of Eldh's [6] 52 cases of nonspecific reactions, sore throat was the only abnormal physical finding, with the exception of the elevation of temperature. In no case was the organism producing the sore throat mentioned. It is possible that our cases 8 and 9 belong in the same group with these 9 just mentioned.

Infectious mononucleosis has repeatedly been reported as a cause of false positive serologic reactions for syphilis. The following authors have reported from 1 to 6 cases each: Löhe and Rosenfeld,[12] Radford and Rolleston,[13] Weber,[14] Weber and Bode,[15] Bernstein,[16] Priest,[17] Wawersig,[18] Hatz [19] and Sadusk.[20] Gooding [21] discussed the main

12. Löhe, H., and Rosenfeld, H.: Ueber Monozytenangina mit anschliessendem vorübergehend seropositiven Erythema nodosum, zugleich ein Beitrag zur Differentialdiagnose zwischen luetischer und nichtluetischer Angina, Dermat. Ztschr. **53**: 373 (April) 1928.

13. Radford, M., and Rolleston, J. D.: Two Cases of Glandular Fever Simulating Typhus, Lancet **2**:18 (July 5) 1930.

14. Weber, F. P.: Glandular Fever and Its Lymphotrophic Blood Picture, M. Press **130**:65 (July 23) 1930.

15. Weber, F. P., and Bode, O. B.: Beiträge zum "Drusenfieber," München. med. Wchnschr. **78**:1589 (Sept. 18) 1931.

16. Bernstein, A.: Antibody Response in Infectious Mononucleosis, J. Clin. Investigation **13**:419 (May) 1934.

17. Priest, R.: Glandular Fever, J. Roy. Army M. Corps **65**:159 (Sept.) 1935.

18. Wawersig, R.: Ueber unspezifisch-positiven Ausfall der Luesreaktionen im Serum bei der Monozytenangina, Med. Klin. **33**:1737 (Dec. 28) 1937.

*(Footnotes continued on next page)*

clinical and laboratory features of 27 cases of infectious mononucleosis and stated:

> The Wassermann reaction and the Sigma and Kahn reactions show many interesting features. For the first three to four weeks of the illness 16 of the 27 cases gave either a positive or incompletely positive Wassermann reaction. Those cases which showed a negative Wassermann reaction, in most instances showed a positive Kahn test. The Sigma test, however, was mostly negative.

Poole and Findlay [22] stated, "The Wassermann reaction is positive in about half the number of cases. It usually becomes positive in the second week, persists for some weeks and then becomes negative." Bernstein [23] reported positive serologic reactions for syphilis in 6 of 37 cases of infectious mononucleosis. He was unable to find any correlation between the results of the Paul-Bunnell test and the serologic reactions for syphilis. Wassermann titers were tabulated in the 6 cases; in 1 instance the titer was as high as 150 units. In a later article, completely reviewing the subject of infectious mononucleosis, Bernstein [24] stated that of the 44 patients he had seen, 18 per cent of those for whom serologic tests were performed had biologic false positive reactions. He expressed the belief that the positive reaction is transitory, rarely occurs over a period longer than three months and generally reverts to negative before the end of the third week of the disease.

Case 11.—A single white man aged 20, a laboratory assistant, had worked for six months prior to the present illness as an animal boy in the medical school. On Oct. 3, 1937, while cleaning a rat cage, he was bitten on the ring finger of the left hand by a large rat. Within a few days the wound became infected, and on October 6 he noted red streaks running up his hand and forearm. At this time he came to the surgical accident room for treatment and was given 1,500 U. S. P. units of tetanus antitoxin. On admission to the hospital, on October 6, the temperature was 99.4 F. The results of serologic tests for syphilis were negative at this time. The rat bite was treated by soaking, and the local infection subsided. On October 11, the patient's temperature rose to 104.4 F., and a maculo-

19. Hatz, B.: The Wassermann Reaction in Infectious Mononucleosis, with a Report of a Case with Unusual Clinical Features, Am. J. Clin. Path. **8**:39 (Jan.) 1938.

20. Sadusk, J. F.: Temporarily Positive Kahn and Wassermann Reactions in Infectious Mononucleosis: Report of a Case, J. A. M. A. **112**:1682 (April 29) 1939.

21. Gooding, S. E. F.: On Glandular Fever or Infectious Mononucleosis, Practitioner **127**:468 (Oct.) 1931.

22. Poole, L. T., and Findlay, H. T.: Laboratory Diagnosis of Glandular Fever (Infectious Mononucleosis), J. Roy. Army M. Corps **66**:145 (March) 1936.

23. Bernstein, A.: False-Positive Wassermann Reactions in Infectious Mononucleosis, Am. J. M. Sc. **196**:79 (July) 1938.

24. Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85 (Feb.) 1940.

papular rash developed, predominantly on the feet, elbows and wrists and to a lesser extent on the knees, thighs and forearms. There were a few scattered lesions over the skin of both flanks and over the back. Several of the lesions contained small vesicles. The epitrochlear and the axillary glands were palpable on the left side. Except for the rash and a soft, short systolic murmur heard at the cardiac apex and transmitted to the base of the heart, the physical findings were essentially irrelevant.

On Oct. 6, 1937 the white blood cell count was 14,000; the hemoglobin concentration, 14.7 Gm. per hundred cubic centimeters, and the differential count, 87 per cent neutrophils and 13 per cent monocytes. On October 12 the white cell count was 8,600, and the differential count, 16 per cent juvenile neutrophils, 48 per cent neutrophils, 1 per cent eosinophils, 26 per cent lymphocytes and 9 per cent monocytes. On October 10 the results of serologic tests for syphilis were negative; they were also negative when repeated on October 14. On November 1, however, the Eagle flocculation test and the Wassermann test both gave positive results.

TABLE 11.—*Serologic Tests for Syphilis, Case 11*

| Date | Laboratory | Wassermann | Eagle Microflocculation | Clinical Findings |
|---|---|---|---|---|
| 10/ 3/37 | .. | .. | .. | Finger bitten by rat |
| 10/10/37 | 1 | .. | 0 | Slight fever; local lesion healed |
| 10/14/37 | 1 | .. | 0 | Fever; maculopapular rash |
| 11/ 1/37 | 1 | P | P | Slight fever; rash disappeared Oct. 28; |
| 11/ 3/37 | 1 | P | P | neoarsphenamine started Nov. 2 |
| 11/ 8/37 | 1 | D | D | Well |
| 11/15/37 | 1 | 0 | D | |
| 11/23/37 | 1 | 0 | P | Relapse; chills |
| 1/ 6/38 | 1 | 0 | 0 | |
| 3/ 7/38 | 1 | 0 | 0 | |
| 2/ 6/39 | 1 | .. | 0 | Well |
| 3/ 7/39 | 1 | 0 | 0 | |
| 4/11/39 | 1 | 0 | 0 | |

Unsuccessful attempts were made to demonstrate Spirochaeta morsus muris in the blood by dark field examination. Mice were given injections of the patient's blood, but S. morsus muris could not be recovered. The rash disappeared October 28, and the patient became afebrile November 8. He was given 0.3 Gm. of neoarsphenamine on November 2 and again on November 9; the dose was increased to 0.6 Gm. on November 16. He was discharged from the hospital at this time, apparently asymptomatic. His temperature was normal, and he felt strong again. He returned to the hospital on November 22 complaining of chills, fever and weakness. His temperature at this time was 104.6 F. Undoubtedly he had a relapse. Physical examination showed nothing abnormal. He was given 0.6 Gm. of neoarsphenamine on November 22 and on December 3, 10 and 24. There was no relapse after this treatment. Serologic tests are summarized in table 11.

Although S. morsus muris was not isolated from the patient's blood in this case, the clinical picture was typical of rat bite fever.

There is some difference of opinion as to whether biologic false positive reactions to serologic tests for syphilis occur in rat bite fever.

Bayne-Jones,[25] in reviewing 81 cases reported in the United States from 1839 to 1930, stated:

> It has often been said that the Wassermann reaction is positive in rat-bite fever. . . . The results of this test were recorded in eighteen cases. Of these, fifteen were negative and three were positive. In each of these three cases, there was the possibility of a coincident syphilis.

On the other hand, Clément[26] found positive results in 14 of 26 patients whose serum was tested for syphilis. He expressed the opinion that this proportion of positive results was too high to be interpreted as the result of coincidental infection with rat bite fever and syphilis. Laignel-Lavastine and his associates[27] reported a case of rat bite fever in which the blood Wassermann reaction was positive during the febrile period of the disease and became negative within a few days after the temperature returned to normal. The Wassermann reaction of the cerebrospinal fluid was repeatedly negative. Labougle[28] reported 1 case of rat bite fever in which there was a false positive reaction for syphilis. Edelman and Haber[8] reported the cases of 3 children with rat bite fever and false positive serologic reactions for syphilis. The family of each child was carefully investigated and was found to be nonsyphilitic.

Woolley[29] reported 1 case, that of a child who had several positive reactions to Hinton tests during the course of the febrile period of rat bite fever. The family of this child was also investigated; the mother and father did not have syphilis. Ledingham[30] reported 5 cases of rat bite fever. Serologic tests for syphilis were done in 3 cases, and in only 1, the case of a child whose mother and father did not have syphilis, was there a biologic false positive reaction.

## COMMENT

These 11 examples of positive serologic reactions occurring in patients with diseases other than syphilis have been selected from a series of approximately 200 such cases observed by us during the past fifteen

25. Bayne-Jones, S.: Rat-Bite Fever in the United States, Internat. Clin. **3**:235 (Sept.) 1931.

26. Clément, R.: Contribution à l'étude des spirochétoses, le sodoku, Thesis, Paris, 1923, p. 72.

27. Laignel-Lavastine, Boutet and others: Un cas typique de sodoku à Paris, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:105 (Feb.) 1924.

28. Labougle: Eléments d'observation complémentaires au sujet d'un cas de spirochétose par morsure de rat (sodoku): (Wassermann; formules sanguines), Soc. de méd. mil. franç., Bull. mens. **19**:14 (Jan.) 1925.

29. Woolley, P. V.: Rat-Bite Fever: Report of a Case with Serologic Observations, J. Pediat. **8**:693 (June) 1936.

30. Ledingham, R. S.: Rat-Bite Fever (Sodoku): Report of Five Cases, Am. J. Clin. Path. **8**:333 (May) 1938.

years. The conditions reported are a subacute infection of unknown cause (case 1), acute labyrinthitis of unknown cause (case 2), vaccinia (case 3), pneumonia (caused by Pneumococcus type IV in case 6 and by an undetermined agent in cases 4, 5 and 7), sore throat of unknown cause (cases 8 and 9), infectious mononucleosis (case 10) and rat bite fever (case 11).

Quantitative titrations of reagin content were performed in 16 cases. The titer was low (1 to 16 units) in 4 and high in 2 (cases 5 and 8). In both of the latter cases, the serum reagin titer on one occasion was 100 units, a titer comparable with that observed in the early stages of syphilis.

Our material clearly offers no clue to the incidence of biologic false positive serologic reactions in conditions or diseases other than syphilis. Indeed, for lack of serial (preferably daily) testing in cases of acute infectious diseases, this type of information is not available for any disease except malaria.

Justification for the publication of such a heterogeneous series of case reports as this lies in the fact that attention is once again directed to the nonspecificity of serologic tests for syphilis and to the caution necessary in their interpretation. This nonspecificity extends to nearly all the usual serologic technics, e. g., in the cases here reported, the complement fixation (Wassermann) and the flocculation (Kahn, Kline, Eagle, Hinton and Laughlen) tests. Not included in this statement, however, is the complement fixation test with spirochetal antigen (recorded in the tables as "pallida" test), which has as yet not been adequately studied with reference to nonsyphilitic diseases. There is already evidence that the reaction to this test is usually negative in cases of leprosy, in which other serologic reactions are positive,[31] but that in cases of malaria it is usually positive simultaneously with other positive serologic reactions.[32] In 2 of our patients (cases 5 and 10) the pallida reaction was negative at a time when other serologic reactions were positive. The "pallida" test may, like the Kahn verification test,[33] prove useful in the differentiation of positive serologic reactions due to syphilis and those due to other conditions.

---

31. Cappelli, E.: La "pallidareazione" di Gaehtgens sui sieri lebbrosi; contributo allo studio dell'essenza della r. Wassermann, Gior. di batteriol. e immunol. **22**:425 (March) 1939. Eagle, H.; Hogan, R. B.; Mohr, C. F., and Black, S. H.: On the Reactivity of the Serum and Spinal Fluid of Leprous Patients with Spirochetal Suspensions, Am. J. Syph., Gonor. & Ven. Dis. **25**:397 (July) 1941.

32. Heinemann, H.: Untersuchungen mit der Pallidareaktion, Dermat. Wchnschr. **94**:680 (May 14) 1932; Ueber die praktische Brauchbarkeit der Pallidareaktion im Arbeitskreis des Tropenarztes, Arch. f. Schiffs- u. Tropen-Hyg. **36**:9 (Jan.) 1932.

33. Kahn, R. L.: A Serologic Verification Test in the Diagnosis of Latent Syphilis, Arch. Dermat. & Syph. **41**:817 (May) 1940.

It seems only fair to suggest that in the absence of a healthy skepticism as to the specificity of serologic tests for syphilis, several at least of the patients whose cases are here reported might well have been given unnecessary treatment for syphilis.

Biologic false positive serologic reactions occurring not only in persons with nonsyphilitic diseases but in normal persons as well [34] require particular emphasis in view of the ever increasing use of routine serologic tests in medical practice, industry and compulsory premarital and antepartum examinations.

SUMMARY

We have reported the cases of 11 nonsyphilitic patients with various diseases in whom transitory biologic false positive serologic reactions for syphilis were observed.

When analyzed quantitatively, a low titer was usually revealed in these tests, but in the tests on 2 patients, 1 with a sore throat and 1 with pneumonia, a high titer, comparable to that seen in the early stages of syphilis, was observed.

It is suggested that a complement fixation test with spirochetal antigen (pallida test) may be helpful in differentiating false from true positive reactions.

In view of the enormous increase in the routine use of serologic tests for syphilis, the necessity for caution in their interpretation is emphasized.

34. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: I. Occurrence in Normal Persons, Arch. Int. Med. **68**:898 (Nov.) 1941.

# PULMONARY CAVITATION ASSOCIATED WITH COCCIDIOIDAL INFECTION

WILLIAM A. WINN, M.D.
Medical Director, Tulare-Kings Counties Joint Tuberculosis Hospital
SPRINGVILLE, CALIF.

That the roentgenographic appearance of pulmonary coccidioidal infection may closely simulate that of pulmonary tuberculosis has been pointed out repeatedly, particularly by Smith,[1] Yegian and Kegel [2] and Farness and Mills.[3] When pulmonary cavitation occurs the mimicry is even more striking, and confusion in diagnosis may follow unless the causative organism is first isolated and identified. It would appear, however, that such parallelism between the two infections exists only in roentgenograms. Coccidioidal cavitation, as demonstrated in the 13 cases reported in this paper, is far more benign than is pulmonary cavitation due to tuberculosis. Unlike the latter condition, which usually occurs during reinfection or in the adult type of the disease, most coccidioidal cavitation develops during or shortly after the primary stage of pulmonary infection. This belief was also expressed by Farness and Mills in their first report of a case of pulmonary cavitation due to coccidioidal infection.

The prognosis in cases of primary coccidioidal cavitation is entirely favorable. Prolonged hospitalization or care in a sanatorium is unnecessary, and patients with this condition may be returned early to unrestricted lives and permitted to continue with their usual occupations, despite the existence of a typical "burned out," or pathologically latent, pulmonary coccidioidal cavity. It is especially important not to resort to extraordinary collapse procedures or thoracic surgery in attempting to close such cavities. Exception may be made and pneumothorax performed if hemoptysis occurs frequently or in large amounts or if the primary cavitation may appear to be in a more active phase than the characteristic thin-walled, residual cavities described here.

---

1. Smith, C. E.: Parallelism of Coccidioidal and Tuberculosis Infections, read at the Clinical Section at the Annual Meeting of the California Tuberculosis Association, April 5, 1941.

2. Yegian, D., and Kegel, R.: Coccidioides Immitis Infection of the Lung, Am. Rev. Tuberc. **41**:393 (March) 1940.

3. Farness, O. J., and Mills, C. W.: Coccidioides Infection, Am. Rev. Tuberc. **39**:266 (Feb.) 1939.

From the standpoint of public health, patients with coccidioidal infection cannot be considered a menace to society, as are those with tuberculosis. Investigators are in general agreement that infection is produced by the chlamydospores of the fungus (reproductive cycle). Acute infection does not pass from person to person via sputum containing the endospores or spherules (parasitic phase). The natural occurrence of the fungus in the soil of areas in which this disease is endemic has been demonstrated. When climatic conditions favor the formation of dust and winds (dry seasons), the infectious chlamydospores, being numerous and light, are easily transported and inhaled and may produce respiratory infection in nonimmune persons. Occasionally, the infectious agent may enter via cuts or abrasions of the skin.

From the clinical standpoint there is striking absence of severe constitutional symptoms despite the existence of pulmonary cavitation, hemoptyses or spherule-laden sputum, so that again one recognizes a paradoxic relation between coccidioidal cavitation and symptomatology.

It is therefore important to bear in mind the possibility of coccidioidomycosis whenever pulmonary cavitation occurs and tubercle bacilli have not been demonstrated, especially when the patient has resided in an area where the disease is endemic. Such regions at present are the San Joaquin Valley and nearby valleys in central California, parts of Arizona and Texas and the Chaco regions of Argentina. Increasing ease of travel and shifting populations will undoubtedly produce a proportionate increase in cases of coccidioidomycosis elsewhere than in these areas.

Acute primary coccidioidomycosis (San Joaquin fever, valley fever, desert rheumatism) was described by Dickson and Gifford in 1938 [4] and its epidemiology presented by Smith in 1940.[5] The extent of coccidioidal infection among the residents of the San Joaquin Valley is indicated by the large proportion of the population giving a positive cutaneous reaction to coccidioidin. Gifford [6] and her associates, who carried out an extensive skin-testing survey in the schools in Kern County, Calif., found that over half of 2,718 children gave a positive cutaneous reaction. The percentage rose from 17 per cent for those with residence under one year to 77 per cent for those with residence of ten years or more. In the town of Maricopa, where most of the children tested were native, 84 per cent reacted. Of 110 students of the Porterville High School freshman class, 76 (70 per cent) reacted to coccidioidin. Of this

4. Dickson, E. C., and Gifford, M. A.: Coccidioides Infection (Coccidioidomycosis), Arch. Int. Med. **62**:853 (Nov.) 1938.

5. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum, Am. J. Pub. Health **30**:600 (June) 1940.

6. Gifford, M. A.: Coccidioidomycosis, Kern County, Session on Fungus Infections, Proc. Sixth Pacific Sc. Cong., 1939, p. 74.

number, only 1 gave a history of erythema nodosum; there was no evidence of coccidioidal granuloma.

Definite evidence of such widespread primary coccidioidal infection, with the probable exception of calcification, is difficult to obtain by an ordinary roentgen examination of the chest. In this respect there exists the same difficulty one encounters in identifying primary tuberculous infection. However, when primary pulmonary coccidioidal infection is manifested by residual cavitation, it should be easily recognized by fluoroscopy alone.

That residual pulmonary coccidioidal cavitation must be regarded as only an infrequent manifestation of the primary coccidioidal infection is borne out by six years' experience in fluoroscopic and roentgen examination of many residents of San Joaquin Valley. However, one must acknowledge that in an unknown number of cases the primary coccidioidal cavities close spontaneously, as illustrated in 4 of the cases reported. Pulmonary cavitation associated with early primary coccidioidomycosis must, therefore, occur more often than would be indicated by the small percentage of latent pulmonary cavities discovered among Valley residents. Coccidioidal granuloma remains a relatively uncommon disease and must not be confused with primary coccidioidomycosis. Pulmonary cavitation in association with granuloma is unusual. There should be no difficulty in differentiating between the two diseases or between the forms of cavitation associated with them.

Primary infection by Coccidioides immitis is commonly accompanied by symptoms referable to the respiratory tract, usually bronchitis with a slightly productive cough. Associated with these may be malaise, anorexia, chills, fever, headache, backache, night sweats and pleurisy. Roentgenograms of the lungs taken at this stage may reveal only changes in the area of the lung root, such as peribronchial haziness, or there may be definite patches of pneumonitis, which often assumes a nodular form. Occasionally, exudative lesions involving lobules, or even entire lobes of the lung, are present and may be associated with early cavitation. Recovery is followed by a walling off or clearing of the primary focus without complication. Evidence of the first infection may remain and be revealed in the roentgenogram in the form of localized caseous or calcified foci or cavitation. Bacteriologic studies of the sputum during the acute stage of the disease will reveal the presence of the spherules of C. immitis. Seven to fourteen days after such infection has occurred cutaneous sensitivity to coccidioidin will develop. In 2 to 5 per cent of the cases erythema nodosum or erythema multiforme will occur, usually appearing five to fourteen days after the onset and persisting for one to four weeks. Occasionally, pleurisy with effusion occurs and the organism can be recovered from the pleural fluid. That primary infection is possible with few or no recognizable symptoms is also to be

accepted, as indicated by the high percentage of reactors to coccidioidin among residents of San Joaquin Valley.

As has been stated, there may be few or no symptoms associated with residual coccidioidal pulmonary cavitation after the acute primary infection has subsided. For this reason 2 cases (1 and 4) were discovered only by chance. When cavitation occurs in conjunction with the acute primary infection (case 11), the clinical picture differs little from the one just described. However, in most (9 of 13) of the cases in this series the patients gave a definite history of hemoptysis, varying from frequent streaking to frank hemorrhage, which caused them to seek medical advice. In 2 cases pulmonary bleeding followed moderately severe physical exertion. In others it was apparently aggravated by acute infection of the lower respiratory tract. In about half of the cases there was a history of one or more respiratory infections, occasionally resulting in a fairly prolonged period of cough and expectoration. Chronic expectoration often appeared as only a slight amount of mucoid material raised in the morning, which increased during respiratory infections or "colds" and then was occasionally streaked with blood. That involuntary or unrecognized production of sputum occurred is illustrated in case 3, in which gastric lavage was necessary to demonstrate the fungus. All patients with latent cavitation (cases 1 to 10) appeared in good health. While they were under observation in the hospital they had no persistent elevation of temperature, pulse rate or respiratory rate. They were able to follow ordinary occupations except when forced to stop work because of recurrent pulmonary hemorrhage (cases 5 and 9).

In describing these cavities the term "latent" has been used to imply that the lesion is no longer progressive but has become arrested and quiescent. The term "healed" could not be applied because these cavities harbor viable C. immitis. Immunity must be produced in the host by the primary infection. Otherwise, because of the prevalence of coccidioidal infection, residents of San Joaquin Valley would invariably die after fairly short stays in the valley. This concept explains best the paradox of persisting pulmonary coccidioidal cavitation without dissemination of the disease, despite the role played by the cavity as a reservoir or incubator for the causative fungus.

Criteria for the diagnosis of latent coccidioidal pulmonary cavitation were based on the roentgenographic appearance of a thin-walled cavity, which appeared "punched out" or "dead," with little or no surrounding collateral reaction. An accompanying clinical history of hemoptysis and occasional infection of the lower respiratory tract, with a slightly productive cough, was usually obtained from the patient, who otherwise seemed well. Cutaneous sensitivity to coccidioidin was demonstrated in all cases

by the intracutaneous test.[7] Careful bacteriologic studies of sputum or gastric contents by Dr. C. E. Smith and associates,[8] of the Department

7. The cutaneous test was made, read and recorded by the method used for the Mantoux tuberculin reaction. The peak of reaction generally occurs thirty-six hours after injection of coccidioidin; in this study the reading was made at the end of forty-eight hours. The result has the same significance as the result of the tuberculin test; i. e., a positive reaction indicates present or past infection with C. immitis.

The coccidioidin used in testing was prepared by Dr. C. E. Smith. The synthetic medium (containing but 2.5 per cent glycerin) approved by the Bureau of Animal Industry was inoculated with multiple strains of C. immitis. After incubation at 37 C. for two months it was made up to volume with one-tenth its volume of a solution of merthiolate and distilled water (1:1,000), filtered through a Berkefeld or Seitz filter and tested for sterility and potency.

Dilutions from 1:10,000 to 1:100 were used, according to the reaction produced. Control tests were also made to rule out sensitivity to glycerin or to other material contained in the medium. Great caution was observed in using needles, syringes and sterilizing pans that had never been used for tuberculin testing. The test is highly specific with dilutions down to and including 1:100. For patients with granuloma it may finally be necessary to use a dilution of 1:10, and terminally patients with this condition may become anergic.

8. Absolute proof of the presence of C. immitis, according to Smith and co-workers (Smith, C. E.; Wheatlake, R. J.; Chern, N.; Lack, A. R., and Baker, E. E.: Diagnosis of Coccidioidal Infection by Recovery of Coccidioides Immitis, to be published), is provided by (1) observation in tissue sections of characteristic double-contoured spherules with endospores and without budding and (2) recovery of the mycelial form by culture and demonstration of spherules in inoculated animals. The following method was used: Sputum, gastric contents or contaminated pus is treated with a 0.05 per cent solution (final concentration) of cupric sulfate. (To prevent solution of spherules gastric contents should be neutralized if allowed to stand for any length of time. Alkaline digestants used in concentrating specimens also rapidly dissolve the endospores.) After it has stood four hours, the suspension is centrifuged. The sediment is examined microscopically in a fresh cover slip preparation and is planted on Sabouraud's medium (to which has been added a 0.05 per cent solution of cupric sulfate) and on a blood agar plate. (A differential medium which was found useful consists of 1 per cent ammonium chloride, 1 per cent sodium acetate, 0.8 per cent tribasic potassium phosphate, 0.04 per cent cupric sulfate and 2 per cent agar.) The plates are incubated at 37 C., and the sediment is placed in the ice box. If the blood agar shows a few colonies the next day the sediment is suspended in a solution of sodium chloride and inoculated intratesticularly into a guinea pig. If many colonies appear, another blood agar plate is inoculated and the procedure is repeated the following day.

The guinea pig is killed after one month (after two weeks if the testicle becomes enlarged), and tissues are examined for spherules and cultured on Sabouraud's medium and/or on the differential medium. If the guinea pig tissues are negative for C. immitis but the culture shows a growth of white fungus suspiciously like coccidioides, the fungus is suspended in a saline solution and inoculated into a guinea pig intratesticularly or a mouse intraperitoneally. The lungs and the omentum should be examined with great care if a mouse is used.

Hanging drop preparations of spherules are also useful for observing their characteristic method of sprouting.

of Public Health, Stanford University School of Medicine, disclosed the presence of C. immitis. Serologic studies of the blood were usually confirmatory.[9] In no case did clinical observation or roentgen follow-up studies, varying from a few months to several years, disclose any evidence of dissemination of the infection or progression of the disease (cases 1 to 13).

## REPORT OF CASES

CASE 1.—C. M., a 19 year old single Portuguese farm worker, had been a resident of Kings County (San Joaquin Valley) since birth.

*First Admission* (April 8, 1936 to May 16, 1937).—The patient had been in generally good health until Jan. 13, 1936, when, after an automobile accident, he noted persistent pain in the right side of the chest and went to his family physician for examination. After roentgen examination of the chest the patient was informed that he had tuberculosis. There was no history of chronic cough or expectoration, although a short time previous to admission he had raised a small amount of sputum in the early morning. He stated the belief that he had had some thoracic pain on the right side previous to the accident and also that he had been tiring more than usual and that his strength was not as good as usual. His physician had reported a temperature of 99 to 100 F. in the afternoon, with a pulse rate of 78 to 90 beats per minute. The patient was referred to the hospital at Springville and admitted on April 8.

Past History: The patient had had the usual childhood diseases. He had never had erythema nodosum or erythema multiforme and to his knowledge had never been exposed to tuberculosis.

Physical Examination: The patient was a well developed, swarthy youth who did not appear acutely ill. No abnormal thoracic signs could be elicited. For the first few weeks the temperature was elevated in the afternoon to a maximum of 100.2 F.; the pulse rate varied from 64 to 90 beats per minute.

Examination of the blood revealed the red cell count was 4,930,000, the white cell count 11,950, with 72 per cent polymorphonuclears and 28 per cent lymphocytes, and the hemoglobin concentration (Tallqvist) 100 per cent. Both the red and white cells were normal in appearance. The Wassermann reaction of the blood was negative on April 11. Five specimens of sputum, including a concentrated twenty-four hour specimen, were negative for tubercle bacilli. Previous to admission, a single specimen of sputum had been reported by the patient's local physician as negative for tubercle bacilli.

A roentgenogram of the chest (fig. 1*A*) taken by the local physician on March 2, prior to admission, revealed a cavity measuring 5 cm. in diameter beneath the right infraclavicular area, with considerable surrounding reaction. This was interpreted as a tuberculous cavity, with surrounding tuberculous infiltration of exudative type. A second roentgen examination approximately five weeks later, following admission, again disclosed the cavity, now smaller, with much less surrounding reaction (fig. 1*B*).

---

9. The serologic tests were performed by Dr. Smith and his associates, who used coccidioidin as an antigen. The results of the serologic studies, which will be reported in another paper, indicate that complement is fixed in a high titer in cases of coccidioidal granuloma but is fixed only in low dilutions in cases of latent coccidioidal pulmonary cavitation. Precipitins, also, give only a low grade reaction in cases of the latter disease.

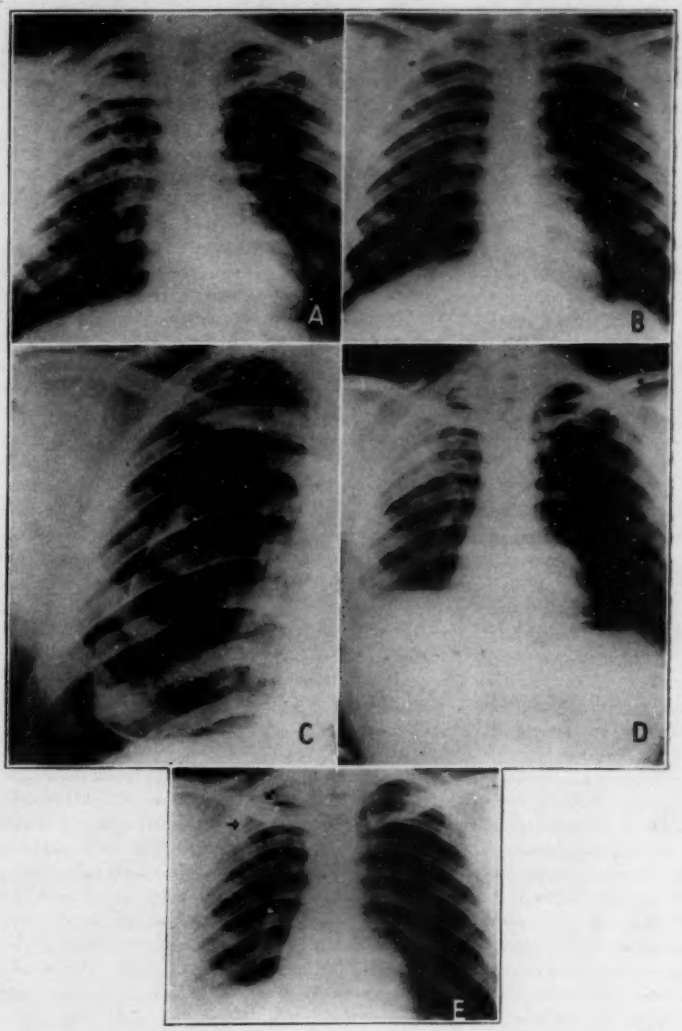



Fig. 1.—Case 1 (C. M.). Roentgenograms taken (*A*) March 2, 1936, (*B*) April 9, 1936, (*C*) Dec. 3, 1937, (*D*) May 15, 1940 and (*E*) Nov. 20, 1940.

Course of Illness: The patient was confined to bed, and despite the absence of tubercle bacilli in the sputum, pneumothorax treatment was started on the right side on April 9. A fairly selective collapse of the upper lobe was obtained, but the previously described cavity remained, with little evident change in size; complete collapse was prevented by a long broad adhesion beneath the second interspace. Peripheral reaction about the cavity was only slight. Because of the failure of the cavity to close, the right phrenic nerve was crushed on August 2; subsequently the right side of the diaphragm rose approximately one interspace.

Discharge: The patient left the hospital on May 16, 1937, with his clinical condition entirely quiescent. He had gained 11¾ pounds (5.4 Kg.) in weight. Pneumothorax refills were continued in the outpatient clinic.

Second Admission (Jan. 18, 1938 to April 6, 1939).—Because the cavity failed to close under this collapse therapy, the patient was advised to reenter the hospital. A roentgenogram (fig. 1 *C*) taken Dec. 3, 1937 disclosed the degree of collapse and the patent cavity. While at home he had been doing general ranch work and had not kept regular hours of rest.

He was again confined to bed, and treatment with pneumothorax under moderately positive pressure was instituted. The cavity failed to close, although the patient's clinical condition remained quiescent, without elevation of temperature or pulse rate. On numerous occasions the sputum, examined both by direct smear and by concentration, was negative for tubercle bacilli.

On March 12, 1938, intrapleural pneumolysis was done and the previously described adhesion successfully severed. Despite a regimen of modified rest in bed and continuation of treatment with pneumothorax under slightly positive pressure the cavity remained open. Roentgenograms showed the cavity lying near the periphery of the relaxed upper lobe of the right lung. Severing the adhesion had in no way aided the effectiveness of the collapse.

In September 1938, consultation with Dr. Leo Eloesser was held concerning the necessity of any further surgical treatment, and it was agreed, in view of the inability to demonstrate tubercle bacilli, that the possibility of a solitary pulmonary cyst should be considered. Mantoux tuberculin tests made then with old tuberculin in a dilution of 1:10,000 produced a 2 plus reaction. It was decided to abandon pneumothorax, and the lung was allowed to reexpand slowly. The cavity remained open beneath the outer infraclavicular area and possessed a thin wall, with no surrounding reaction.

The patient was discharged from the hospital on April 6, 1939, and the diagnosis was changed to one of "no definite evidence of pulmonary tuberculosis; probable solitary pulmonary cyst." He was seen at intervals of three months and remained in good health, doing ranch work involving heavy labor. Fluoroscopic and roentgen examination revealed little change in the appearance of the cystlike cavity.

He remained well until May 15, 1940, when he acquired a "chest cold" and a productive cough, which forced him to stop work and resulted in the loss of approximately 11 pounds (5 Kg.) of weight and the onset of easy fatigability. A roentgenogram (fig. 1 *D*) taken May 15 revealed considerable new exudative reaction occupying the upper half of the right pulmonary field and surrounding the cystlike cavity.

*Third Admission* (May 17 to Aug. 6, 1940).—He was again admitted to the hospital and was placed on a regimen of modified rest in bed. Neither the temperature, the pulse rate nor the respiratory rate was elevated. A slightly productive cough was present. He stated that the "cold" had improved considerably and that he "was getting over an attack of influenza." A roentgenogram taken three weeks later showed clearing of the exudative reaction. The cavity remained

and apparently contained fluid. On June 9 the patient gave a 2 plus cutaneous reaction to coccidioidin in a dilution of 1:1,000. Stained preparations of sputum remained negative for tubercle bacilli. A specimen of sputum collected on May 24 was reported by Dr. Smith to contain C. immitis; a white fungus morphologically like coccidioides was recovered from sputum cultured on several different mediums, from the spherules of C. immitis found in large testicular lesions of a guinea pig inoculated with treated sputum and killed June 11 and from spherules found in the lungs of a mouse inoculated with the fungus recovered in the guinea pig.

The patient was discharged to his home on August 6, with the diagnosis "primary coccidioidomycosis, with cavitation."

Roentgen examination on November 20 revealed the clearing about the cavity, which retained its characteristic thin-walled appearance.

On November 26 a sample of blood serum preserved with merthiolate was sent to Dr. Smith, who reported: "Complement was completely fixed in the second tube (1:4) and partially fixed in the next tube."

When next seen in the outpatient clinic, on Jan. 20, 1941, the patient stated that he felt in good health and was again able to work about the ranch. His weight had increased to 186½ pounds (84.7 Kg.). He had had no cough, expectoration or recent "colds" or "influenzal attacks." A roentgenogram taken with the patient in a slightly oblique position revealed the persistence of the cavity in the apex of the right lung, with little change in size, shape or appearance.

When the patient was seen again, June 25, roentgen examination (fig. 1*E*) failed to reveal further evidence of the cavity in the apex of the right lung. It had apparently closed spontaneously. Clinically the patient remained well and continued to work. There had been no further infection of the upper respiratory tract.

The roentgenographic appearance of the cavity so closely simulated that of cavitation in a case of tuberculosis that the patient was energetically treated for a long period in a tuberculosis hospital. Recognition of the cavity as one of coccidioidal type was not made until C. immitis was demonstrated in the sputum, approximately four years after the patient first came under medical observation. This case also illustrates exacerbation about the cavity, associated with the presence of spherules in the sputum and followed by rapid clearing of the reaction in ten weeks. At the end of five and a half years' observation (September 1941) the pulmonary coccidioidal cavity has apparently closed spontaneously.

CASE 2.—E. D., a 21 year old single American, an ex-enrollee of the Civilian Conservation Corps and telephone construction helper, had resided in Visalia (Tulare County) for seventeen years.

*Hospitalization* (July 21, 1939 to July 31, 1940).—The patient had been in general good health until one month prior to admission, when he noticed a warm sensation in his throat and without warning coughed up approximately 1 to 2 drachms (4 to 7 cc.) of red blood. The hemoptysis gradually cleared in the course of the next twenty-four hours. For the year and half previous to admission he had noticed slight shortness of breath on exertion and had complained of occasional night sweats. There was no history of chronic cough, expectoration, influenzal attacks, valley fever or erythema nodosum. To his knowledge he had

not been exposed to tuberculosis. His weight had remained fairly stable, at 130 pounds (59 Kg.). He had been referred to the hospital by his physician because of the hemoptysis.

Past History: The past history was irrelevant.

Physical Examination: The patient was a tall, thin, fairly well developed young man who was obviously not ill. Examination of the chest revealed nothing abnormal. The temperature, pulse rate and respiratory rate were within normal limits. Examination of the blood yielded the following data: red cell count, 4,200,000; white cell count, 6,550, with 64 per cent neutrophils, 33 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils; hemoglobin content, 11.5 Gm. per hundred cubic centimeters, and Kline reaction of the blood negative.

A roentgenogram (fig. 2*A*) taken prior to admission, July 8, revealed a prominent cavity in the extreme apex of the left lung, above the clavicle, with little surrounding reaction. The remainder of the lung parenchyma appeared to

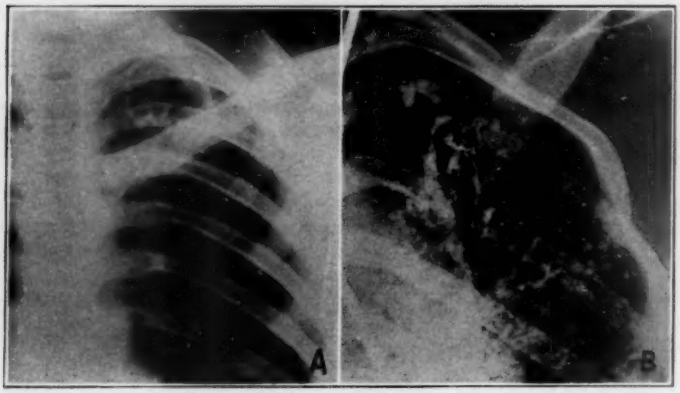



Fig. 2.—Case 2 (E. D.). Roentgenograms taken (*A*) July 8, 1939 and (*B*) Feb. 22, 1940.

be clear. A presumptive diagnosis of pulmonary tuberculosis was made on the basis of this roentgenogram.

Course of Illness: On admission the patient was confined to bed. There was no chronic cough, although occasionally he raised a small amount of mucoid sputum, not more than 0.5 drachm (1.9 cc.) per twenty-four hours. On a few occasions this was found to be blood streaked. On numerous occasions the sputum, including concentrated specimens and material obtained by gastric lavage, was negative for tubercle bacilli. Likewise, examination of moist preparations of sputum failed to reveal spherules of C. immitis. The patient gave a negative cutaneous reaction to intracutaneous tests with old tuberculin in a dilution as low as 1:100 and to purified protein derivative (second strength). On August 19 he gave a 2 plus reaction to coccidioidin in a dilution of 1:1,000. Unneutralized gastric contents obtained on November 30 were sent to Dr. Smith. Because C. immitis could not be demonstrated by direct examination, culture or animal inoculation, the specimen was recorded as negative for this organism on Jan. 4, 1940.

Because of the apical cavitation in the left lung, initial pneumothorax had been started on July 25, 1939. In the next few weeks only a partly effective collapse

was obtained, with the lung remaining suspended at the apex by a few pleural bands. The collapse was continued with refills of 350 to 400 cc. of air, and the patient was permitted modified exercise. After five months a roentgenogram revealed the cavity in the apex was still open, with little decrease in size. On December 29 the patient had a small hemoptysis. The ineffective pneumothorax was discontinued in January 1940. The diagnosis of tuberculosis had not been confirmed, and the existence of another pathologic condition was considered. Throughout repeated examinations in January and February the sputum remained negative for tubercle bacilli. On February 22 iodized poppyseed oil was instilled into the bronchus of the upper lobe of the left lung through a ureteral catheter, with the patient in the horizontal and in the Trendelenburg position. The oil was seen to enter the ascending bronchial tree, then flow into a curious, bluntly dilated saccule, which seemed to be curved on itself and was surrounded by a faintly visible peripheral zone forming a halo (fig. 2*B*). Apparently the oil had flowed in and partly filled a loculated cavity which lay in the extreme upper part of the lobe.

A second specimen of sputum, collected on February 5, was forwarded to Dr. Smith. He and his associates isolated C. immitis both by culture and by animal inoculation.

On March 8 a single specimen of sputum prepared by the cover slip method revealed a few double-contoured bodies typical of C. immitis. On April 4 the patient had an acute attack of pleurisy at the base of the left lung, which subsided in a few days under conservative treatment. During the remainder of the period of hospitalization he showed little clinical change and resumed exercise.

He was discharged to the outpatient department on July 31. When seen again, on October 8, he had gained in weight and had been working in a garage. One episode of infection of the upper respiratory tract had occurred, associated with cough and production of sputum but with no further hemoptysis. A roentgenogram taken at that time showed persistence of the previously described cystlike cavity in the apex of the left lung, with little change elsewhere in either pulmonary field.

A specimen of sputum taken on Jan. 21, 1941, was forwarded to Dr. Smith, who again isolated C. immitis. The patient continued his work in the garage and felt well. A roentgenogram taken January 21 showed only a suggestion of the cavity remaining in the extreme apex of the left lung.

He was last seen on June 21. The pulse rate and temperature were normal. There had been no further cough or production of sputum. Roentgen examination of the chest revealed a small amount of residual fibrosis persisting in the apex of the left lung. The cavity could no longer be outlined and was apparently closed.

The appearance of the cavity in the first roentgenogram, taken July 8, 1939, was typical of latent coccidioidal cavitation. The history of hemoptyses was also suggestive. Instillation of iodized poppyseed oil revealed the trabeculated structure of the cavity and indicated associated bronchial changes. The patient gave negative cutaneous reactions both to old tuberculin and to purified protein derivative. The cavity has apparently closed with the patient under a normal routine of working and living, approximately two years after he first came under roentgen observation. Failure to neutralize the specimen of gastric contents on Nov. 30, 1939 permitted the solution of any spherules present, and C. immitis was not isolated until Feb. 5, 1940.

CASE 3.—F. R., a 37 year old American housewife and office worker, had lived in Tulare County (San Joaquin Valley) for fifteen years.

*First Admission* (July 24 to Sept. 6, 1938).—Seven years before admission the patient had been in an automobile accident and had never felt well since. In May 1931 a cough had developed, which was followed by three pulmonary hemorrhages, during which she had raised from 0.5 to 1 ounce (15 to 30 cc.) of blood. A consultant in San Francisco, to whom her local physician had mailed roentgenograms, had advised that she had bronchopneumonia. She had been confined to bed, where she had remained for six months with steady improvement. The only further symptom had been occasional pain in the right side of the chest which was unrelated to respiration. Thereafter, she had been able to carry on with her ordinary daily duties, including employment as a secretary. There had been no chronic cough or expectoration, but she had noticed blood-tinged sputum on several occasions during "chest colds." At these times she had had some pain in the right side of the chest. She had been referred to the hospital at Springville by her local physician.

Past History: The patient gave a history of influenza in 1922.

Family History: The family history was irrelevant, and to her knowledge she had never been exposed to tuberculosis. She had not had erythema nodosum or erythema multiforme.

Physical Examination: The patient was a thin, apprehensive woman who was not in distress. The left shoulder drooped somewhat. One examiner heard occasional rales in the right axilla, but this was not noted again. Studies of the blood revealed the red cell count was 4,720,000, the white cell count 7,300, with 78 per cent neutrophils, 20 per cent lymphocytes, 2 per cent eosinophils and no monocytes or basophils, and the hemoglobin concentration (Sahli) 98 per cent. The red cells appeared normal; the Kline reaction was negative and the sedimentation curve and rate (Brooks) were normal.

A roentgenogram (fig. 3*A*) taken June 11 revealed an elongated, well defined, annular cavity lying beneath the third interspace on the right side, with little surrounding reaction; elsewhere the pulmonary fields were comparatively clear.

Course of Illness: The patient was placed on a regimen of modified rest in bed. Her temperature, pulse rate and respiratory rate remained within normal limits. There was no cough or production of sputum. Except for occasional restlessness she seemed comfortable.

It was felt that the diagnosis lay between a quiescent tuberculous cavity in the base of the right lung and a congenital solitary cyst. Sputum was not available for study. A roentgenogram taken August 11 failed to reveal any change in the appearance of the cavity in the right lung. At her own request the patient was discharged from the hospital on September 6 for continued observation in the outpatient department.

Eight months later she stated that she felt fine and had been generally well. A roentgenogram revealed little change in the appearance of the cystlike cavity in the right lung. There was no evidence of surrounding inflammatory reaction. The patient gave a negative cutaneous reaction to old tuberculin in a dilution of 1:1,000 and a positive reaction (3 plus) to coccidioidin in a dilution of 1:10. The tests with these substances were repeated Dec. 29, 1940, at which time the patient gave a negative reaction to old tuberculin in a dilution of 1:100 and a positive reaction (1 plus) to coccidioidin in a dilution of 1:1,000.

*Second Admission* (April 3 to 7, 1940).—Iodized poppyseed oil introduced through a bronchial catheter only partly filled an irregularly shaped bronchial defect in the approximate location of the cystlike cavity (fig. 3*B*).

She returned to the outpatient clinic on December 29, at which time she stated that she had been feeling well except for a slight attack of influenza in November, which had resulted in a slightly productive cough. A roentgenogram revealed little change in the size, shape or appearance of the cystlike cavity.

Dr. C. E. Smith commented as follows on a specimen of gastric contents taken April 6, 1941: "Cultures on Sabouraud's and on a special differential coccidioides medium yielded a growth of white fungus resembling coccidioides. A white mouse inoculated with the culture on April 9 died May 7, with many pulmonary lesions containing endosporulating spherules. Cultures from the lesions showed a growth of characteristic white fungus on differential coccidioides medium. It is concluded that the specimen submitted contained viable C. immitis."

On April 28 Dr. Smith reported the following results of serologic tests: "Complement fixation test: dilution of 1:2, 4 plus; dilution of 1:4, 1 plus. Precipitin test: undiluted, 1 plus; dilution of 1:10, questionable. The serum shows evidence

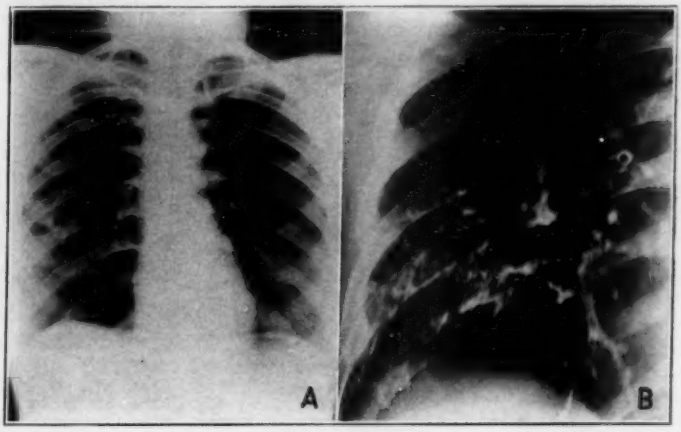



Fig. 3.—Case 3 (F. R.). Roentgenograms taken (*A*) June 11, 1938 and (*B*) April 4, 1940.

of infection with C. immitis to the degree characteristically seen in patients with a solitary cavity."

A roentgenogram of the chest taken September 24 revealed persistence of the cavity and little change in its appearance. The patient declared that she felt well, had no symptoms of involvement of the respiratory tract and continued to work.

During a period of thirty-eight months' roentgenographic observation the typical thin-walled appearance of the latent coccidioidal cavity remained unchanged. The cavitation produced few symptoms other than the hemoptyses previous to observation and interfered in no way with the patient's occupation. In this case, also, the use of iodized poppyseed oil revealed an associated, localized and minor bronchial defect. The result of the complement fixation test was indicative of a mild, latent infection. C. immitis was isolated from neutralized gastric

contents both by culture and by animal inoculation. The patient gave a negative cutaneous reaction to old tuberculin in a dilution of 1 : 100 and a positive cutaneous reaction to coccidioidin in a dilution of 1 : 1,000.

CASE 4.—J. H., a 24 year old single American-born Mexican ex-enrollee of the Civilian Conservation Corps and ranch worker, had been a resident of Kings County (Hanford) for eleven years.

*First Admission* (April 12 to Nov. 30, 1940).—The patient had no specific complaints. He was seen in the chest clinic as a contact who had been exposed to possible tuberculous infection through a tuberculous sister. Fluoroscopic examination had revealed a small cavity in the middle of the left pulmonary field, and the patient had been referred to Springville for hospitalization. On closer questioning, he described occasional pain of two or three months' duration in the left side of the chest and stated he had lost 4 to 5 pounds (2 to 2.5 Kg.) in weight. There was no definite history of cough, expectoration or hemorrhage.

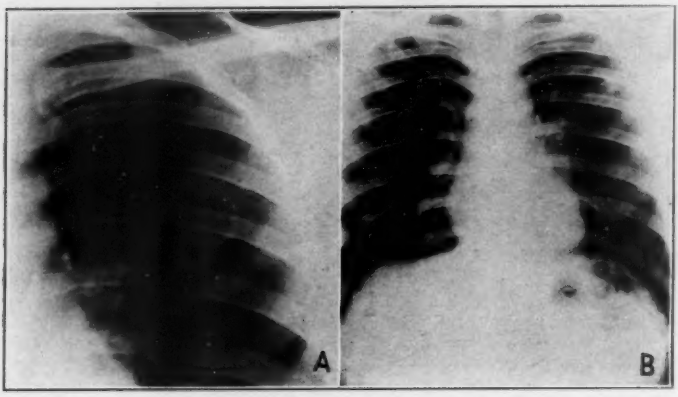



Fig. 4.—Case 4 (J. H.). Roentgenograms taken (*A*) April 2 and (*B*) Aug. 24, 1940.

Past History: The patient had had the usual childhood diseases. He had not had valley fever or erythema nodosum or other cutaneous rash.

Family History: In 1939 a sister, aged 29 had died of pulmonary tuberculosis. The patient had had definite contact with her.

Physical Examination: The patient was a healthy-appearing, well nourished man who was obviously not ill. Examination of the chest revealed nothing abnormal except a few inconstant fine rales beneath the left second intercostal space anteriorly. Studies of the blood on admission revealed that the Kline reaction was negative, the hemoglobin content 14 Gm. per hundred cubic centimeters, the red cell count 5,140,000 and the white cell count 9,350, with 65 per cent neutrophils, 31 per cent lymphocytes, 3 per cent eosinophils and 1 per cent monocytes.

A roentgenogram (fig. 4 *A*) taken at the time of the first examination, April 2, disclosed a distinct, thin-walled cavity, approximately 3 cm. in diameter, beneath the third rib on the left, with little peripheral reaction. A few small calcified foci were noted adjacent to the right descending bronchial tree and in the left hilus.

Course of Illness: After admission the patient was placed on a regimen of modified rest in bed.

On numerous occasions material obtained by gastric lavage, concentrated sputum and sputum inoculated on Petragnani's culture medium were negative for tubercle bacilli.

On April 19 he gave a 2 plus cutaneous reaction to old tuberculin in a dilution of 1: 10,000. On June 7 he gave a 1 plus cutaneous reaction to coccidioidin in a dilution of 1: 1,000.

Cover slip examination of sputum forwarded to Dr. Smith September 13 revealed a few double-contoured, endosporulating spherules. No tubercle bacilli were seen. Cultures and animal inoculations confirmed the presence of C. immitis.

Dr. Smith commented as follows on the results of serologic studies: "Complement fixation test: dilution of 1:2, 2 plus. Precipitin test: unsatisfactory. Because of the fatty character of the serum, the precipitin tests gave unsatisfactory results. The low titer of complement fixation and the questionable precipitin reaction are characteristic of quiescent coccidioidal infection associated with solitary cavity."

Serial roentgenograms taken during the patient's stay in the hospital revealed little change in the appearance of the cystlike cavity (fig. 4 *B*). His temperature, pulse and respiration remained normal. On November 7 iodized poppyseed oil introduced directly into the main primary bronchus through a ureteral catheter failed to fill any defects in the area of the cavity. Apparently there was no sufficiently large bronchial communication, as the bronchial tree itself was well outlined and showed no evidence of pathologic change. He was discharged on November 30, with a diagnosis of latent coccidioidal cavitation.

On Jan. 21, 1941, he stated that he had been entirely well after returning home. Sputum was present only occasionally and in slight amounts. Roentgen examination revealed the persistence of the cystlike cavity in the left infraclavicular area, with little evidence of surrounding reaction.

He was last seen on September 16, at which time he felt entirely well and had been working in the fields. The cavity could no longer be outlined either by fluoroscopic or by roentgenographic examination. It had closed spontaneously, leaving only a small area of fibrosis.

A typical latent coccidioidal cavity was discovered during a routine examination of contacts with a patient known to have tuberculosis. The reactions both to coccidioidin and to tuberculin were positive. The importance of distinguishing between the two types of cavitation is apparent. The patient was kept under roentgenographic observation for eighteen months; final closure of the cavity occurred under normal living and working conditions.

CASE 5.—C. H., a 28 year old married white American service station worker, had been a resident of Kings County (San Joaquin Valley) for ten years.

*First Admission* (April 28 to May 15, 1939).—The patient had been referred to the clinic at Springville by his local physician because of frequent blood spitting for approximately two years. Four days before examination he had raised about 1 ounce (30 cc.) of red blood in association with a severe attack of coughing. Otherwise, he felt well and did not complain of weakness, loss of strength or easy tiring. There was no history of chronic cough or expectoration, although the patient stated that occasionally he coughed and raised "some" sputum. No history of thoracic pain or unexplained fever was elicited.

Past History: The patient had had the usual childhood diseases. He had not had any recent attacks of influenza or severe infections of the respiratory tract. No history of erythema nodosum or erythema multiforme was obtained.

Family History: The patient's mother died at the age of about 35 of tuberculosis following childbirth. At this time he was ten years old. There was no other history of tuberculosis in the family.

Physical Examination: The patient was well nourished and appeared to be in good health. The chest was entirely normal. Studies of the blood revealed that the

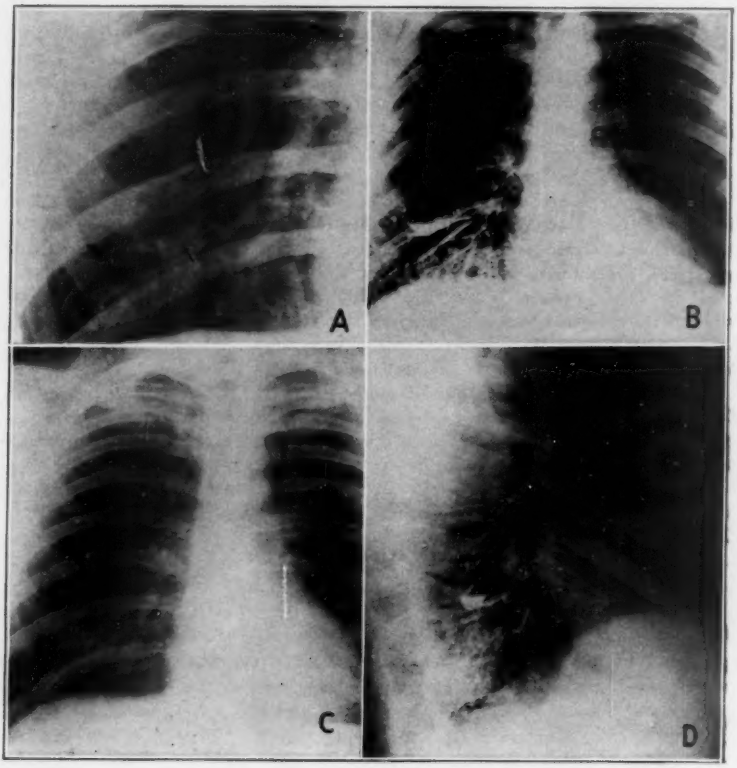



Fig. 5.—Case 5 (C. H.). Roentgenograms taken (*A*) April 19, 1939, (*B* and *C*) May 11, 1939 and (*D*) Feb. 3, 1941.

sedimentation (Brooks) was normal, the Kline reaction negative, the hemoglobin content 16.5 Gm. per hundred cubic centimeters, the red cell count 5,120,000 and the white cell count 7,100, with 74 per cent neutrophils, 25 per cent lymphocytes and 1 per cent eosinophils. During the patient's entire stay in the hospital there was no elevation of temperature or abnormality of pulse or respiration.

Course of Illness: Roentgenograms (fig. 5 *A*) taken April 19 in the outpatient department had been interpreted as follows: "A thin-walled cavity in the right

pulmonary field beneath the fourth interspace measures approximately 3.5 cm. in diameter. The pulmonary fields are comparatively clear aside from a slight amount of peribronchial haziness adjacent to the descending right bronchial tree. In a right lateral view the same annular shadow appears in the lower lobe posterior to the root of the lung."

Shortly after admission blood-tinged sputum was obtained and was found negative for tubercle bacilli. The cutaneous reaction to old tuberculin in a dilution of 1 : 10,000 was 1 plus and to coccidioidin in a dilution of 1 : 10 was 3 plus. On May 12, 2 guinea pigs were inoculated with digested and concentrated sputum. Neither gave any evidence of a pathologic condition when killed six and eight weeks later, respectively. Just before death both gave negative reactions to 0.1 of old tuberculin in a dilution of 1 :100.

Bronchoscopic examination on May 11 failed to reveal pathologic changes in the larynx, trachea or primary bronchial tree. A smear of material obtained direct from the bronchus was negative for tubercle bacilli. With the patient under fluoroscopic observation, iodized poppyseed oil introduced into the lower lobe of the right lung through a ureter catheter outlined the bronchial tree and then pooled in the bottom of the cavity (fig. 5 *B*). The structure communicated with a fairly large bronchial branch, and this connection could be visualized easily in the lateral view with the patient in the vertical position (fig. 5 *C*). There was no evidence of other pathologic change in the bronchial tree.

The patient was discharged from the hospital with a diagnosis of a latent pulmonary coccidioidal cavity, without evidence of pulmonary tuberculosis. He was advised to refrain from work for several months.

Ten months later he stated that he had been working in a service station since the previous August and had been in good health. "Occasional color" had been noted in small amounts of sputum raised after severe physical effort. The roentgenographic appearance of the cystlike cavity was unchanged. He was advised to continue with his work.

He was next seen on Oct. 23, 1940, when he stated that two weeks previously a heavy truck tire, which he had been changing, had slipped off the wheel and struck him heavily on the chest. Two hours later he had had a sudden hemorrhage in association with severe coughing, and had raised approximately a half cupful of bright red blood. The hemorrhage had continued throughout the next few days, with the amount of bleeding gradually subsiding and the blood becoming darker. There had been no associated fever, chills or thoracic pain. He had returned to Springville on the advice of his physician. The roentgenographic appearance of the cavity in the base of the right lung was little changed at this time. A specimen of sputum obtained during the few days following this visit to the clinic and examined both by direct smear and by concentration was negative for tubercle bacilli. Petragnani's medium inoculated with sputum failed to yield any growth after four months. During two hours of observation the sedimentation curve (Cutler) of the blood was normal, or quiescent. C. immitis was isolated by culture and by animal inoculation, with both mycelial growth and spherules, from a specimen of sputum obtained October 25. Mycobacterium tuberculosis was not isolated.

The patient was advised to refrain from all work for three months and to follow a regimen of rest. On Jan. 10, 1941, when he reported to the outpatient department, he stated that small pulmonary hemorrhages had occurred after any severe exertion. He had experienced the last one, ten days previous to examination, after carrying a heavy tub of water into the back yard. This effort had

been followed by a coughing spell, and the sputum had contained considerable red blood. In roentgenographic appearance the cavity in the base of the right lung was approximately unchanged in size and shape. Because of the continued bleeding the patient was advised to return to the hospital for institution of pneumothorax.

*Second Admission* (Jan. 27 to Feb. 24, 1941).—He was placed on a regimen of modified rest in bed and initial pneumothorax was established on the right side on January 30. During the stay in the ward he was noted to have occasional slight cough productive of less than 1 drachm (3.7 cc.) of slightly mucoid sputum every twelve hours. Definite double-contoured spherules, resembling C. immitis, were demonstrated in a moist preparation of sputum examined January 29. No tubercle bacilli could be observed in preparations treated with acid-fast stain. Dr. Smith commented as follows on a specimen of blood serum: "There were no demonstrable precipitins. Complement fixation was complete in the first tube (dilution of 1:2) and partial in the second tube (dilution of 1:4); it was clear thereafter."

After establishment of pneumothorax therapy the patient was discharged from the hospital. The cystlike cavity appeared to be closing (fig. 5*D*).

On May 21 he stated that he had been generally well. A small amount of bloody sputum had been expectorated for two days of the preceding week. Pneumothorax refills were continued twice a week in order to obtain an effective collapse. Fluoroscopic examination revealed moderate expansion of the lung and the continued presence but reduced size of the cavity.

At his last examination, on September 8, he appeared well. Roentgen examination disclosed a good collapse on the right side. The previously described cavity in the base of the right lung could no longer be visualized.

In this case of latent coccidioidal cavity of the lung, pneumothorax therapy was given because of the history of frequent hemoptyses. The patient could not retain employment because of these episodes, which had been witnessed by his employer. The cavity had an open bronchial communication, and therefore collapse therapy was effective, as indicated by the last roentgenogram. The robust, healthy appearance of the patient since the time of his first examination, despite the cavity and the hemoptyses, is worthy of note. Over two years' roentgenographic observation the cavity did not change, nor was there any tendency for the infection to disseminate, despite the frequent and considerable pulmonary bleeding. Digestion of the sputum in May 1939 by sodium hydroxide, the customary procedure previous to concentration, destroyed any spherules present and prevented isolation of the fungus. Alkaline digestants rapidly dissolve the endospores. In October C. immitis was found by Dr. Smith in sputum which had not been previously treated with sodium hydroxide. The cavity has apparently been closed by pneumothorax.

CASE 6.—W. B., a 36 year old married American farm laborer, was born in Texas and had resided in Kings County (San Joaquin Valley) for five years.

*First Admission* (Nov. 15, 1940 to Jan. 28, 1941).—The patient had been referred by his physician to the chest clinic because of a slightly productive chronic cough of one year's duration. At times he had noticed some streaks of blood in the sputum

and pain, which was variable and was aggravated by deep breathing, both on the left and on the right side of the chest. He had lost strength, and his weight had decreased from 170 to 155 pounds (77.1 to 70.3 Kg.) in the last year. On closer questioning he stated that he might have had a slight cough for a number of years.

Past History: No history of valley fever, erythema nodosum or other cutaneous rash could be elicited. The patient had had no definite exposure to tuberculosis, although 1 sister, who died at the age of 33, was suspected of being "tuberculous."

Physical Examination: The patient was a large well developed, swarthy man who did not appear ill. His skin was somewhat loose, suggesting recent loss of weight. The chest appeared symmetric and expanded well and equally on the two sides. The only definite abnormality was a slight increase in the spoken

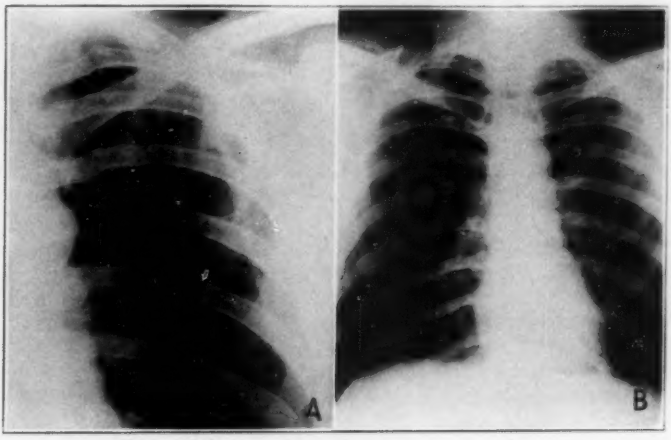



Fig. 6.—Case 6 (W. B.). Roentgenograms taken (*A*) Nov. 6, 1940 and (*B*) April 8, 1941.

voice over the left axilla. Studies of the blood yielded the following data: red cell count 4,460,000, white cell count 9,800, with 58 per cent neutrophils, 32 per cent lymphocytes, 7 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils, hemoglobin concentration (Tallqvist) 85 per cent red cells and platelets normal. The Kline reaction of the blood was negative.

Roentgen examination in the outpatient department on November 6 disclosed a thin-walled cavity, measuring approximately 4 by 5 cm., beneath the left infraclavicular area and near the periphery of the lung (fig. 6*A*). There was a slight amount of surrounding reaction, and increased markings extended outward from the hilus toward the cavity. The pleura in the right costophrenic angle and an interlobar septum in the middle of the right pulmonary field were thickened. The clinical impression was that of a latent coccidioidal cavity of the lung.

Course of Illness: The patient was permitted restricted physical activity and given a high caloric diet. His temperature, pulse rate and respiratory rate remained within normal limits.

A specimen of sputum collected on November 6 was reported two months later by Dr. Smith to be positive for C. immitis and negative for Myco. tuberculosis. Mycelial growth had been demonstrated in cultures, spherules in inoculated animals and mycelial growth in cultures of tissues from these animals.

Cutaneous reactions to tests, made November 16, were as follows: coccidioidin (1:1,000), 1 plus; coccidioidin control, negative, and old tuberculin (1:100,000), 1 plus. Two specimens of sputum collected over seventy-two hours and concentrated and 1 specimen sent to the state laboratory were negative for tubercle bacilli. Cultures planted on Petragnani's medium were negative for growth.

The report of the serologic studies ran as follows: "Complement fixation test: dilution of 1:2, 3 plus, and dilution of 1:4, 1 plus. Precipitin test: undiluted, negative. The low titer of complement fixation and the questionable precipitin reaction without evidence of active infection are characteristic of the quiescent coccidioidal infection associated with solitary cavity."

On November 19 a roentgenogram taken in the left lateral view disclosed the previously described cavity in the upper lobe of the left lung, posterior to the hilus. Roentgen examination on Jan. 25, 1941, shortly before the patient's dismissal from the hospital, revealed the thin-walled cavity in the left infraclavicular area. The cavity was somewhat smaller than it had appeared in the original roentgenogram, and there was less surrounding reaction. Elsewhere the pulmonary fields remained perfectly clear.

On discharge from the hospital the patient had gained 24 pounds (10.9 Kg.) in weight and looked generally improved. He was advised to return to his former occupation.

*Follow-Up Observation.*—On April 8 he returned to the clinic. He stated that he had had three "colds," associated with slightly productive cough, at different times since dismissal from the hospital. Otherwise he felt well and intended to work. A specimen of sputum sent to Dr. Smith on February 6 by the patient, during a "cold," was found to contain a few viable organisms of C. immitis. Roentgen examination on April 8 showed little change in the appearance of the cavity (fig. 6*B*). A slight amount of peripheral collateral reaction remained, but the pulmonary fields elsewhere were clear.

The patient was last seen on September 20. He had been working in the cotton fields. He felt quite well but complained of two "colds" since the previous examination, associated with the production of 0.5 ounce (15 cc.) of occasionally blood-streaked sputum per day. He also had been bothered with some pain on the left side of the chest related to respiration. Roentgenographic examination of the chest showed that the cavity was unchanged in size, with a small amount of persistent surrounding reaction. Elsewhere the pulmonary fields remained clear.

In this case the catarrhal symptoms, with a more or less chronic productive cough and frequent "chest colds," are predominant. Occasionally the sputum was blood streaked. Despite the presence of pulmonary cavitation and occasional spherule-laden sputum, this man has continued hard physical labor for seven months without ill effect.

CASE 7.—J. C. S., a 27 year old white married American farm worker, had resided in Tulare County (Earlimart) for three years.

*Admission to Hospital* (May 26 to June 29, 1941).—Two years prior to admission the patient had had an attack of "pleurisy" with severe pain beneath the left shoulder blade not definitely related to respiration.

One year ago he had suffered from "influenza," associated with a slightly productive cough, chills and general malaise. One and a half days after his recovery he had begun to cough up bloody sputum during heavy labor. He had stopped work and gone home to bed. The next morning, during severe coughing, he had raised "about a handful of red blood." This bleeding had continued for a week in gradually decreasing amounts, and the blood had become darker, until it disappeared. Roentgen examination by his local physician had revealed nothing abnormal. Since then the patient had had frequent slight hacking cough, aggravated by such factors as hay dust and exertion.

His general health had remained good, and he had been able to work until four weeks prior to admission, when he had again suffered a mild attack of "influenza," associated with fever, a productive cough, general malaise and aggravation of his thoracic pain. He had remained at home only a few days and then returned to his work as a cotton chopper. About this time he had begun to spit up a small amount of blood every morning, which on some occasions amounted to several mouthfuls. He had continued his work despite the blood spitting and

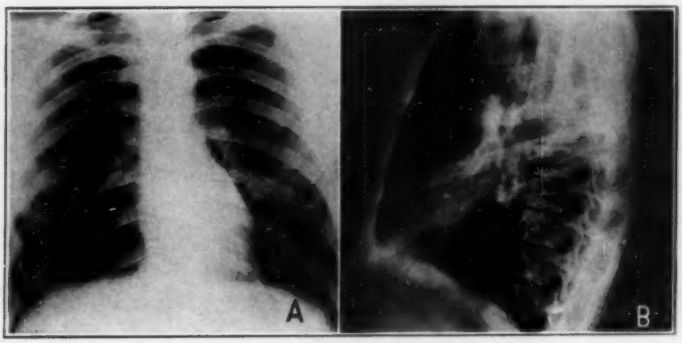



Fig. 7.—Case 7 (J. C. S.). Roentgenograms taken (*A*) May 21 and (*B*) June 16, 1941.

felt fairly well. He had been referred to Springville by State Relief Administration authorities.

Past History: No history of erythema nodosum or erythema multiforme was elicited. One brother had been tuberculous ten years previous but had made a complete recovery; possibly the patient had been exposed to this brother during his illness.

Physical Examination: The patient was rather thin but apparently was healthy. Examination of the chest revealed nothing definitely abnormal.

Studies of the blood yielded the following data: hemoglobin content 16 Gm. per hundred cubic centimeters (94 per cent Sahli), red cell count 4,730,000, white cell count 5,150, with 3 per cent band neutrophils, 71 per cent mature neutrophils, 23 per cent lymphocytes and 3 per cent monocytes, Kline reaction negative and sedimentation curve and rate (Brooks and Cutler) normal.

Roentgen examination during his first visit to the clinic, on May 21, disclosed a thin-walled cavity with little surrounding reaction, measuring approximately 3 cm. in diameter and lying beneath the fourth interspace on the left side (fig. 7 *A*).

Calcified foci were noted in the right pulmonary field. The clinical impression was latent coccidioidal pulmonary cavitation.

Course of Illness: The patient was placed on a regimen of modified rest in bed. He had an occasional slightly productive cough, with sputum amounting to 2 to 3 drachms (7 to 12 cc.) daily. His pulse rate varied from 64 to 98 beats per minute, and the temperature was occasionally elevated to 99 F. On the day of admission the patient gave cutaneous reactions of 1 plus and 2 plus, respectively, to old tuberculin in a dilution of 1 : 100,000 and coccidioidin in a dilution of 1 : 1,000. Many specimens of sputum collected over varying periods and concentrated were examined both by smear and by culture and were negative for tubercle bacilli. Two weeks after admission a few organisms with doubly refractile walls resembling the spherules of C. immitis were noted in a moist preparation of sputum. A few small white colonies, also typical of C. immitis, were produced on Sabouraud's medium inoculated with this sputum.

A second roentgen examination, ten days after the first, revealed no change in the appearance or size of the previously described cavity. In the lateral view the cavity lay slightly below and posterior to the hilus, in the upper portion of the lower lobe (fig. 7 *B*).

A specimen of sputum forwarded to Dr. Smith on June 4 was reported positive for C. immitis. Cultures and animal inoculations confirmed this report.

Both complement fixation and precipitin tests were negative.

The last roentgen examination, made on September 27, showed the cavity in the base of the left lung was unchanged in size, shape and appearance. A small amount of reaction in relation to the bronchial tree remained immediately adjacent to the cavity. A specimen of sputum forwarded to Dr. Smith a few days later was reported to contain viable C. immitis. A few weeks previously the patient had returned to his work as a laborer and had remained generally well.

Pleurisy of two years' duration was marked at the beginning of the second year by an acute episode of what was termed "influenza" but in all probability was primary coccidioidomycosis. This episode was accompanied by hemoptysis, which occurred again one month prior to admission, appearing at daily intervals. The roentgenographic observation of a typical solitary cavity was followed by the demonstration of C. immitis in the sputum. The negative serologic reactions can be disregarded in view of similar negative reports in 2 cases (8 and 9) of known coccidioidal infection.

Case 8.—E. J. T., a 30 year old Texas-born white housewife, had resided in Tulare County (San Joaquin Valley) for four years.

*Admission to Hospital* (April 18 to June 28).—The patient had been in good health until a fortnight before admission, when symptoms of "flu" had developed, with chills, generalized aching pains, malaise and a slightly productive cough. She had remained in bed two days and then, feeling quite well, had resumed her household activities. Approximately ten days later, while ironing clothes, she had suddenly begun to spit up blood. The slight cough associated with the bleeding had lasted for about a half-hour, during which time the patient lost about 2 ounces (60 cc.) of blood. Her physician had advised examination at the hospital in Springville.

She had since been symptom free except for a slightly productive, persistent cough, unassociated with further bleeding.

Past History: No relevant history could be elicited. The patient had not had erythema nodosum or erythema multiforme, had not noticed any loss of weight, strength or physical endurance and had no knowledge of a family history of tuberculosis or of contact with a tuberculous person.

Physical Examination: The patient was well developed and nourished and did not seem ill.

Examination of the chest revealed nothing definitely abnormal.

Course of Illness: The patient was placed on a regimen of modified rest in bed. There was no elevation of pulse rate, temperature or respiratory rate. Examination of the blood revealed the hemoglobin content was 13.5 Gm. per hundred cubic centimeters (79 per cent Sahli), the red cell count 4,500,000 and the white cell count 19,500, with 4 per cent band neutrophils, 70 per cent mature neutrophils,

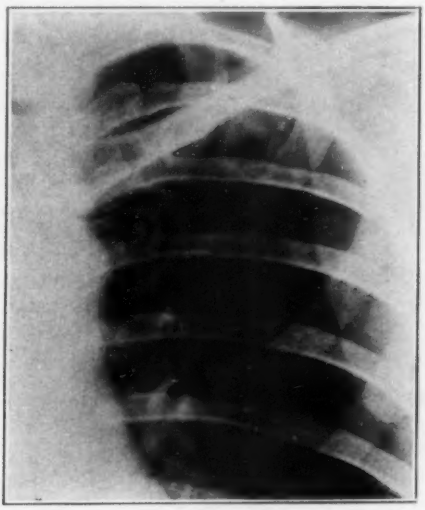


Fig. 8.—Case 8 (E. J. T.). Roentgenogram taken April 16, 1941.

21 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. The appearance of the red cells was normal. About two weeks after admission the red cells were still normal, and the white cell count was 10,250, with 1 per cent band neutrophils, 72 per cent mature neutrophils, 20 per cent lymphocytes, 4 per cent monocytes and 3 per cent eosinophils. The sedimentation rate (Brooks) of the blood was 6 mm. at the end of sixty minutes, and the curve was considered to be normal. Coccidioidin in a dilution of 1:1,000 produced a 1 plus cutaneous reaction, and old tuberculin in a dilution of 1:100 produced a 2 plus cutaneous reaction. The Kline reaction of the blood was negative. She had only a slightly productive cough, and sputum was rather difficult to obtain. Twenty-four to forty-eight hour specimens were collected and concentrated. Neither examination nor culture revealed tubercle bacilli.

A roentgenogram of the chest taken at the clinic prior to admission disclosed in the outer first interspace on the left side a small soft area of infiltration, within which was a cavity approximately 1.5 cm. in diameter (fig. 8). Else-

where the pulmonary fields were comparatively clear. Comparison of this roentgenogram with one taken a week earlier by the patient's local physician disclosed some decrease in the size of the area of infiltration but no evidence of cavitation. The clinical impression was subsiding acute primary coccidioidomycosis, with pulmonary cavitation.

On June 5 Dr. Smith reported that of three specimens of sputum forwarded to him on April 21, April 25 and May 12, the second and third contained C. immitis but were negative for Myco. tuberculosis. These results were confirmed by routine cultural and animal inoculation studies.

Roentgen examination on April 29 showed little change in the appearance of the lesion or the surrounding reaction in the apex of the left lung. Elsewhere the pulmonary fields were clear. The only change revealed by roentgen examination a month later was some decrease in the surrounding reaction.

The patient was allowed to resume physical activity slowly and was discharged to her home seventy-four days after admission, with the advice to return to her ordinary household duties.

The serologic reactions were completely negative.

When she was last seen in the clinic, on August 9, she felt well. Two weeks before she had "spit a small amount of blood." Roentgen and fluoroscopic examination revealed the cavity was still present, little changed in size or appearance since its discovery four months previously.

This case, with a history of an acute illness suggestive of primary coccidioidomycosis and the appearance of cavitation in the apex of the left lung approximately two weeks later, at about the time of the hemoptysis, illustrates, as does case 11, the association of cavitation with primary disease. The negative serologic reactions may be disregarded in view of the isolation of C. immitis from the sputum.

CASE 9.—S. B., a 35 year old married American truck driver, was born in Colorado and had been a resident of Fresno and Kings counties (San Joaquin Valley) for fourteen years.

*Admission to Hospital* (May 29 to June 10, 1941).—In January 1941 the patient had a severe attack of "influenza" and had been in bed for five days, with severe cough, fever and general malaise. The cough had persisted for several weeks. He had then remained in good health until the middle of April, six weeks prior to admission, when one day, after clearing his throat, he expectorated a small amount of red blood. Similar small hemoptyses then occurred daily; they were not particularly related to physical activity. His work was heavy and necessitated driving a large truck. There had been no respiratory symptoms previous to these episodes of bleeding. For months his longest period without hemoptysis was only two days. He had not felt it necessary to consult a physician and had continued with his work of hauling rock. On May 17, after considerable physical effort, he had suddenly raised about two mouthfuls of bright red blood, an amount definitely greater than any previous one. This frightened him, and he consulted a physician, who referred him to the hospital at Springville, after a roentgen examination of his chest. Until admission he had remained in bed at home and had had no further hemoptyses. There were no other complaints and no loss of weight, strength or physical endurance.

Past History: No history of erythema nodosum, erythema multiforme, valley fever, familial tuberculosis or contact with a tuberculous person could be elicited.

Physical Examination: The patient appeared well nourished and healthy. Examination of the chest disclosed nothing abnormal. The temperature, pulse rate and respiratory rate remained within normal limits during the entire period of hospitalization. Studies of the blood yielded the following data: red cell count 5,300,000, white cell count 9,400, with 63 per cent neutrophils, 19 per cent lymphocytes, 15 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils and hemoglobin content 16 Gm. per hundred cubic centimeters. The red cells appeared normal, the Kline reaction was negative and the sedimentation rate (Cutler) was 11 mm. in sixty minutes.

Course of Illness: The patient was placed on a regimen of modified rest in bed. The cutaneous reactions to coccidioidin (1:100) and old tuberculin (1:100) were 3 plus and negative, respectively.

Numerous examinations of sputum, carried out by direct and concentration methods, including cultures and guinea pig inoculations, failed to reveal tubercle

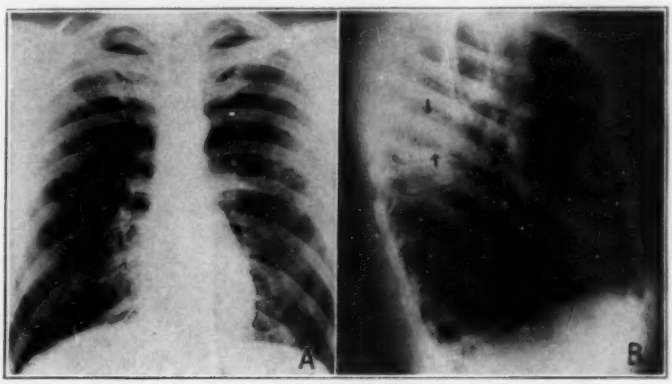



Fig. 9.—Case 9 (S. B.). Roentgenograms taken (*A*) May 29, and (*B*) June 5, 1941.

bacilli. On May 31 several round refractile bodies, slightly larger than lymphocytes and resembling C. immitis, were present in the sputum.

On June 23 Dr. Smith reported that specimens of sputum received on June 2 and 4 were positive for C. immitis. Cultures and animal inoculations had been fully confirmative.

Roentgen examination on May 29 revealed a thin-walled, somewhat elongated cavity, measuring approximately 2 by 4 cm., beneath the third rib on the left side (fig. 9*A*). There was practically no surrounding reaction, and the cavity had a more or less "punched out" appearance. Elsewhere the pulmonary fields were clear. The clinical impression was latent coccidioidal pulmonary cavitation.

About a week later a left lateral view of the chest revealed the thin-walled cavity to be in the upper portion of the lower lobe of the lung, posterior to the root, overlying the middle thoracic portion of the spine and roughly ovoid (fig. 9*B*).

During the stay in the hospital there was no further evidence of hemoptysis, and the patient was discharged to his home. The results of the complement fixation and precipitin tests were negative.

One month after discharge the patient stated that he felt well and had not had cough or pulmonary bleeding. The roentgenographic appearance of the cavity was unchanged.

Repeated hemoptyses finally drew attention to a latent coccidioidal cavity. Despite a long period of pulmonary bleeding the patient continued his work, without reactivation or dissemination of the disease. In this case, as in case 5, physical exertion tended to aggravate the bleeding and forced the patient to stop work temporarily. The negative serologic reactions must be disregarded.

CASE 10.—C. C. G., an 11 year old American-born school girl of Mexican parentage, had resided in Tulare since birth.

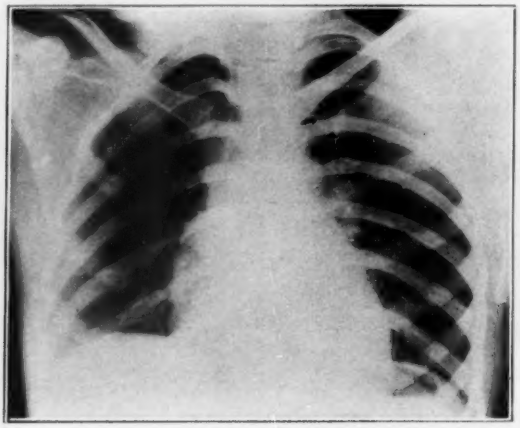


Fig. 10.—Case 10 (C. C. G.). Roentgenogram taken June 14, 1941.

*Admission to Hospital* (May 12, 1941).—The patient was first seen in the outpatient department on April 5, where she was brought by her mother because of persistent cough and expectoration following a severe "cold" of about three weeks' duration and failure to gain in weight. There had also been slight exposure to an aunt who had tuberculosis. The temperature was 98.4 F. and the pulse rate 100 per minute.

Fluoroscopic examination revealed a large annular shadow in the apex of the left lung, adjacent to the mediastinum. It was necessary to rotate the child to bring the cavity into view. The cavity was poorly visible in a roentgenogram taken with the child in the usual posteroanterior position. The pulmonary fields were otherwise clear.

A month later the "cold" had improved and the child felt much better. The cavity in the left apex was still fluoroscopically visible. A roentgenogram disclosed the cavity beneath the sternal end of the first rib on the left side, lying close to the mediastinum and measuring approximately 2 by 3 cm. Although it had a fairly thick wall, there was little surrounding parenchymal reaction. Elsewhere the

pulmonary fields were comparatively clear. The mother was advised to permit the child to be hospitalized for study and observation.

Past History: No history of erythema nodosum or erythema multiforme could be elicited, and otherwise the history was irrelevant.

Physical Examination: On the day of admission to the children's convalescent unit, the child was rather thin, but she was not ill. No abnormal chest signs could be elicited. At the time of the first examination, a month before, rather marked whispering pectoriloquy had been observed in the apex of the left lung and in the left axilla and at the lower border of the left scapula.

Course of Observation: The child was permitted to resume full physical activity after the preliminary routine isolation. There was no elevation of temperature, pulse rate or respiratory rate. The cough had stopped, and sputum was completely absent. Studies of the blood revealed that the Kline reaction was negative, the hemoglobin concentration 16 Gm. per hundred cubic centimeters (91 per cent, Sahli), the red cell count 5,580,000 and the white cell count 6,200, with 1 per cent band neutrophils, 39 per cent mature neutrophils, 51 per cent lymphocytes and 9 per cent monocytes. The appearance of the red cells was normal and the sedimentation rate (Brooks) 4 mm., with a normal curve. The cutaneous reaction to coccidioidin (1:100) was 1 plus, and the cutaneous reactions to old tuberculin (1:100) and purified protein derivative (second strength) were negative. Three specimens of material obtained by gastric lavage were concentrated and examined for tubercle bacilli, both directly and by culture. A portion of each was sent to Dr. Smith. On May 18 specimens of blood serum were forwarded to Dr. Smith for serologic tests. His report on June 6 was as follows: "Complement fixation test: dilution of 1:2, 3 plus; dilution of 1:4, 1 plus, and dilution of 1:8, negative. Precipitin test: undiluted, 3 plus; dilution of 1:10, 1 plus, and dilution of 1:40, negative. The positive result of the complement fixation test and the moderately positive result of the precipitin test are characteristic of the serologic reactions associated with arrested solitary cavity due to C. immitis."

Roentgen examination on June 14 with the child in an oblique anteroposterior position revealed that the previously described cavity had decreased somewhat in size and there was little surrounding reaction (fig. 10). Elsewhere the pulmonary fields remained clear.

At the date of this report (September 18) it has not been possible to recover C. immitis from the gastric contents. The diagnosis of latent primary coccidioidal infection, with pulmonary cavitation, is based on a positive cutaneous reaction to coccidioidin and negative cutaneous reactions to old tuberculin (1:100) and purified protein derivative (second strength). The positive reaction to the complement fixation test was of sufficiently high titer to be significant. Other presumptive evidence is furnished by the typical roentgenographic appearance of the solitary apical cavity and by the clinical history. Actual recovery and isolation of the fungus may have to await the return of an acute episode of respiratory infection, with associated production of sputum. Specimens of sputum obtained in the clinic when the child was first seen were examined in the routine manner for tubercle bacilli only and were negative for these organisms.

CASE 11.—This case is an instance of acute primary coccidioidomycosis, in which it was possible to observe roentgenographically the development of typical pulmonary disease, including the appearance and, three months later, the closure of a solitary apical cavity.

A. P., a 29 year old single Portuguese dairy worker, had resided in Tulare for two years.

*Admission to Hospital* (Feb. 21 to Aug. 17, 1941).—He was first seen in the outpatient department on Feb. 4, 1941. For the two years previous he had felt

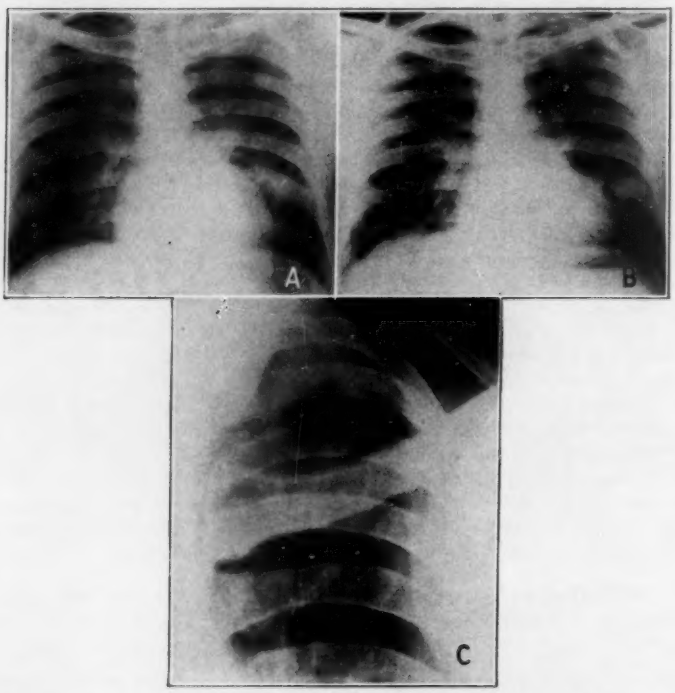



Fig. 11.—Case 11 (A. P.). Roentgenograms taken (*A*) February 4 and (*B, C.*) April 22, 1941.

unwell at times and had noted occasional sharp pain on the left side of the chest, associated with some shortness of breath when he lay on his left side. In November 1940 he had contracted what he thought was a "cold." It had persisted and was associated with severe coughing, expectoration of considerable yellowish sputum, night sweats and occasional hoarseness. Because of these symptoms he had consulted a local physician, who told him after roentgen examination of his chest that he had pulmonary tuberculosis. He believed he had lost 5 to 6 pounds (2.3 to 2.7 Kg.) in weight. However, he had not lost any strength or had hemoptysis and had carried on his work in the dairy.

Past History: The patient had had a severe "cold" of six weeks' duration in 1935, with a productive cough and loss of weight and strength. No history of erythema nodosum, valley fever, tuberculosis in the family or contact with a tuberculous person could be elicited.

Physical Examination: The patient was well developed and muscular and did not appear ill. Slight hoarseness was present, but indirect laryngeal examination failed to disclose any definite pathologic condition. The expansion of the chest was decreased on the left side. Harsh breath sounds were noted at the lower border of the left scapula and in the left axilla, with whispering pectoriloquy at the lower border and just beneath the angle of the left scapula. No rales were heard.

Roentgen examination revealed soft exudative infiltration scattered throughout the left pulmonary field, of fairly marked density in the apex (fig. 11 *A*). The right pulmonary field was relatively clear of infiltration, although there was perihilar haziness. The clinical impression was acute primary coccidioidomycosis.

Course of Illness: The patient was confined to bed. There was no elevation of the temperature, pulse rate or respiratory rate. Two to 3 drachms (7 to 11 cc.) of slightly purulent sputum was raised every twenty-four hours. Studies of the blood yielded the following data: hemoglobin content 17 Gm. per hundred cubic centimeters (100 per cent Sahli), red cell count 5,250,000, white cell count 10,350, with 47 per cent neutrophils, 40 per cent lymphocytes, 9 per cent monocytes and 4 per cent eosinophils, appearance of red cells normal and Kline reaction negative. The following cutaneous reactions were obtained: coccidioidin (1:1,000), 3 plus; coccidioidin control, negative, and old tuberculin (1:10,000), 1 plus. On repeated occasions sputum examined by direct, concentration and culture methods was negative for tubercle bacilli, as was material obtained by gastric lavage and concentrated. Two specimens of sputum taken on March 27 and April 3 were sent to Dr. Smith, who reported on May 10 that both contained viable C. immitis, demonstrated by culture and animal inoculation. On April 23 the sedimentation rate (Brooks) of the blood was 17 per cent at the end of sixty minutes and the resultant curve was interpreted as slightly pathologic.

Blood serum preserved with merthiolate was sent to Dr. Smith, who reported on April 12 as follows: "Complement fixation test: dilution of 1:2, 4 plus, and dilution of 1:4, 1 plus. Precipitin test: undiluted and dilution of 1:10, 1 plus. These results check each other and indicate the mild type of serologic response associated with primary infection which is subsiding or with a solitary cavity, such as has been observed in your patients. The results would not be incompatible with cavity formation, which you believe is occurring."

On March 13 the patient was allowed to resume some physical activity. Roentgen examination of the chest on March 21 disclosed clearing of some of the previously described patchy infiltration on the left side. There remained three rather distinct nodular shadows, one just outside the right hilus and the other two in the left pulmonary field. In the apex of the left lung there was an area of partial atelectasis and within it a rounded area of increased radiability, suggestive of early cavitations.

Apparently the cavity was forming during the active primary infection, and on April 22 roentgen examination of the chest and of the apex of the left lung revealed a definite cavity, measuring approximately 2 cm. in diameter and possessing the thin, "ragged" walls characteristic of a newly formed cavity (fig. 11, *B* and *C*).

The patient continued to improve and was permitted more physical activity. He ceased raising sputum and consistently gained in weight. Roentgen examination

showed the persistence of several small circumscribed nodules outside the right hilus and the continued clearing of the previously described exudative reaction on the left side. The cavity remained; it had changed little in size but possessed the thin wall typical of a latent coccidioidal cavity.

Five weeks later roentgenograms disclosed that the infiltrate on the left had cleared further and that the cavity was no longer present but had apparently closed. Nodular infiltration persisted in the base of the left lung but had become more discrete. These observations were substantiated by fluoroscopic examination.

The patient felt well, was allowed unlimited exercise and had gained 18 pounds (8.2 Kg.) since his admission There was no cough or production of sputum. He was discharged to his home six months after admission.

On October 15, roentgenographic study revealed persistence of two small nodules of infiltration beneath the first and the fourth interspaces on the left side. A small amount of fibrosis remained in the apex of the upper lobe on the left side, the cavity remaining closed. The patient felt "very well."

This case of active primary pulmonary coccidioidomycosis offered the unusual opportunity of watching the development of an associated solitary cavity in the apex of the left lung. The cavity developed despite healing of the general pulmonary infection. Clear evidence is furnished that such cavitation can be an accompanying feature of the primary infection. The cavity persisted for approximately three months and then closed spontaneously.

CASE 12.—This case is an instance of a large coccidioidal cavity associated with chronic symptoms and treated with pneumothorax, with approaching success.

J. C., a 33 year old Texas-born married ranch worker, had resided in Kings County (San Joaquin Valley) for twenty-three months.

*Admission to Hospital* (July 12, 1940 to Jan. 4, 1941).—In 1937 the patient had had a fairly severe attack of "pneumonia" followed by a chronic, productive cough, which in the year previous to admission had become so severe at times as to interfere seriously with his rest at night. Otherwise, he had felt well and had not lost weight or experienced undue fatigue. He had been able to carry on heavy farm labor with difficulty. He had not had thoracic pain or hemoptysis. Because of the chronic cough a roentgenogram (fig. 12*A*) of the chest had been taken on May 21 during a survey by the State Bureau of Tuberculosis and forwarded to the hospital at Springville for interpretation, where a presumptive diagnosis of pulmonary tuberculosis had been made. When the patient first reported to the clinic at Springville, on July 3, another roentgenogram of the chest had disclosed the same large cavity lying outside the right hilus which had been visible in the first roentgenogram. There was a moderate amount of surrounding collateral reaction, and the hilus shadow appeared enlarged. Elsewhere the pulmonary fields remained comparatively clear. Hospitalization had been advised.

Past History: No definite history of valley fever, erythema nodosum, erythema multiforme or exposure to tuberculosis could be elicited.

Physical Examination: The patient was a moderately thin man, with an occasional loose cough, who did not appear ill. The chest was symmetric and expanded equally on the two sides. Resonance was slightly impaired over the right side of the chest anteriorly, and the breath sounds were somewhat louder at

the base of the right lung than at the base of the left one. No definite rales were noted. Studies of the blood revealed the red cell count was 4,340,000, the white cell count 11,550, with 59 per cent neutrophils, 34 per cent lymphocytes, 6 per cent eosinophils and 1 per cent monocytes and the hemoglobin content 15 Gm. per hundred cubic centimeters. The appearance of the red cells was normal.

Course of Illness: The patient was placed on a regimen of modified rest in bed. There were no abnormalities of temperature, pulse or respiration. Pneumothorax on the right side was started immediately because of the size of the cavity. Sputum, amounting to 1 drachm (3.7 cc.) of mucopurulent material during the first week of hospitalization, gradually decreased and completely disappeared at the end of four months.

A roentgenogram taken three weeks after admission with the patient in the right lateral position showed the cavity to be located in the upper portion of the lower lobe. It had become somewhat smaller. Roentgen examination one month

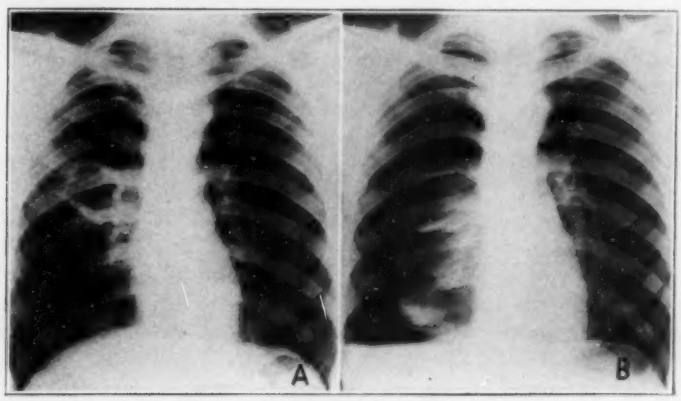



Fig. 12.—Case 12 (J. C.). Roentgenograms taken (*A*) May 21, 1940 and (*B*) June 20, 1941.

after admission with the patient in the posteroanterior position revealed that the pneumothorax on the right side had resulted in a moderate collapse of the lung and decrease in size of the cavity.

On numerous occasions the sputum was examined by direct smear, concentration and culture and was negative for tubercle bacilli. Moist preparations were negative for spherules of C. immitis.

A specimen of sputum referred to Dr. Smith on September 25 was positive for C. immitis and negative for Myco. tuberculosis, and the findings were confirmed by the usual culture and animal inoculation studies.

The following cutaneous reactions were observed: old tuberculin (1:100), negative; purified protein derivative (second strength), negative; coccidioidin (1:1,000), 1 plus, and coccidioidin control, negative.

Dr. Smith reported the following results of serologic tests made with blood serum prepared on November 28: "Complement fixation test: dilution of 1:2, 3 plus. Precipitin test: undiluted, 1 plus. The low titer of the complement fixation

and the questionable precipitin reaction are characteristic of serologic reactions in cases of quiescent coccidioidal infection with associated solitary cavity."

The patient's rapid improvement was manifested by a 15 pound (6.8 Kg.) gain in weight. He was allowed to resume exercise and was discharged to his home on Jan. 4, 1941, to return to the outpatient department for pneumothorax refills at intervals of two weeks. Roentgen examination of the chest shortly before his discharge revealed a good collapse on the right side and a decrease in the size of the cavity.

After discharge the patient remained at home on a regimen of restricted activity. Roentgenograms showed slightly more collapse on the right side and a small amount of fluid in the pleural space. He had occasional expectoration and cough but otherwise felt well. C. immitis was still present in sputum collected on March 16.

He continued to receive pneumothorax refills at intervals of two weeks. The last roentgenogram (fig. 12 *B*), taken on June 20, revealed a good collapse on the right side and a small amount of fluid in the pleural space. The cavity was much smaller, measuring about 1 cm. in diameter.

There has been little change in the roentgenographic appearance of the collapsed lung to date (September 18). The cavity is apparently closing. On July 24 355 cc. of turbid, straw-colored fluid was aspirated from the right pleural space. Bacteriologic studies of this fluid by Dr. Smith failed to yield any growth. Since then there has been no tendency for the fluid to reappear, and a satisfactory collapse has been maintained.

The appearance of the cavity, regardless of its large size, indicated a latent infection associated with chronic productive cough. Effectiveness of pneumothorax in closing the cavity cannot be completely evaluated at this date, although the decrease in size is promising. Spherule-laden sputum will probably remain until complete closure and healing are obtained.

CASE 13.—This case illustrates the occurrence of localized bronchiectatic change, rather than formation of a solitary cavity, due to coccidioidal infection, with the production of symptoms similar to those of cavitation. This case, first recorded in 1930, is the only one of this type encountered.

A. M. P., a 36 year old American widow, had resided in Tulare County (Dinuba and Visalia) for twenty-one years.

*First Admission* (Sept. 12 to Oct. 4, 1930).—The patient had been referred to the sanitarium because of a history of chronic cough of six months' duration and daily expectoration on the average of 0.5 ounce (15 cc.) of purulent sputum, which was frequently blood stained. She also complained of easy fatigability and loss of weight. Roentgen examination revealed a few changes in the apex of the right lung which were interpreted as infiltration with fibrosis, without definite evidence of cavitation (fig. 13 *A*). Moist rales were heard on several occasions over the upper lobe of the right lung. Many specimens of sputum were negative for tubercle bacilli. After one month's observation the patient was discharged, with a presumptive diagnosis of nontuberculous bronchiectasis.

*Second Admission* (Sept. 22 to Nov. 3, 1940).—During the ten odd years following dismissal the patient had been in general good health except for occasional colds, which tended to persist. She had no definite chronic cough, but she

recalled occasionally clearing her throat of a little blood-streaked sputum, especially in the morning. Approximately one week previous to admission she had turned over in bed, suddenly begun to cough and raised about a cupful of red blood. She had gone to her physician the next day and had been referred to the hospital in Springville for examination.

Past History: No history of erythema nodosum, erythema multiforme or definite exposure to tuberculosis could be elicited.

Physical Examination: The patient was a tall, thin woman who was not ill but had an irritating, spasmodic and slightly productive cough. The chest was symmetric, and expansion was equal on the two sides. Resonance was normal. The breath sounds at the apex of the right lung were described as rather harsh and loud as compared with those at the apex of the left lung, and voice sounds were somewhat increased over the first-named area. A few medium rales were heard over the right supraclavicular area. Examination of the blood yielded the following data: Kline reaction negative, hemoglobin content 14 Gm. per hundred

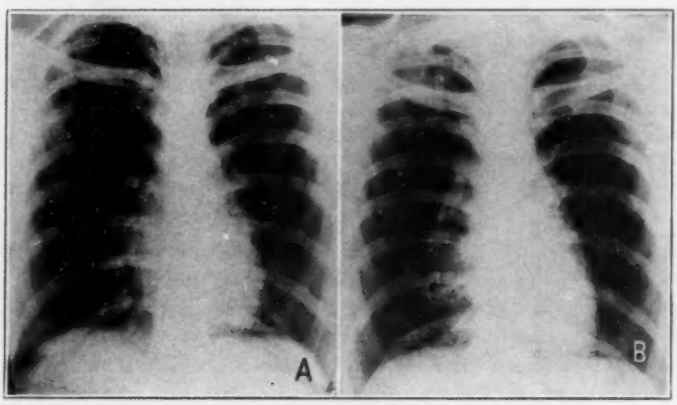



Fig. 13.—Case 13 (A. M. P.). Roentgenograms taken (*A*) Sept. 17, 1930 and (*B*) Sept. 21, 1940.

cubic centimeters, red cell count 4,130,000 and white cell count 8,800, with 66 per cent neutrophils, 27 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The appearance of the red cells was normal.

Course of Illness: The patient was placed on a regimen of modified rest in bed. Her temperature, pulse rate and respiratory rate were within normal limits. Roentgen examination of the chest revealed progressive change in the apex of the right lung since September 1930 which suggested localized dilatation of the apical bronchial tree and associated cavitation (fig. 13 *B*). Elsewhere the pulmonary fields were comparatively clear. On numerous occasions sputum examined by direct smear, concentration and culture was negative for tubercle bacilli. Dr. Smith reported that a specimen of sputum forwarded to him October 2 was positive for C. immitis and negative for Myco. tuberculosis.

The following cutaneous reactions were observed after admission: old tuberculin (1:100), 2 plus; occidioidin (1:1,000), 3 plus, and coccidioidin control, negative.

The results of serologic tests were reported by Dr. Smith as follows: The "complement fixation test revealed a 4 plus binding of complement through dilutions of serum down to 1:40. It was not possible to demonstrate precipitins because of contamination of the serum."

On October 28 iodized poppyseed oil was introduced into the upper part of the right bronchial tree through a small catheter, inserted in the bronchus with the patient anesthetized with pontocaine hydrochloride and maintained in a modified Trendelenburg position. The oil was seen to outline the bronchial tree extending into the upper lobe of the right lung. It flowed into the apex with some difficulty and only partly entered sacculated dilated bronchial defects in the extreme apical region corresponding to the area under observation. The clinical impression was bronchial sacculation and dilatation (bronchiectasis, with cavitation of the apex of the right lung).

Roentgenograms taken after the patient was discharged showed evidence of some residual oil within the alveoli in the right infraclavicular area and no change in the appearance of the pathologic condition in the apex of the right lung; otherwise both pulmonary fields were clear.

When last seen, on June 20, 1941, the patient stated that she had remained well after returning home and complained only of occasional cough and sputum, which had been blood streaked on a single occasion. Her appetite and strength were good, and she had increased in weight to 150 pounds (68 Kg.). Roentgen examination revealed little change in the appearance of the pathologic condition in the apex of the right lung. A small amount of residual poppyseed oil was visible in the outer infraclavicular area. Elsewhere the pulmonary fields were clear.

Indolent apical bronchiectasis existed in the right lung for eleven years. Recovery of viable C. immitis from the sputum and the fixation of complement in fairly high titer identify the causative agent. Over this long period there has been no serious dissemination of the disease from its original focus. As in the cases of cavitation, the condition can best be classified as a latent primary coccidioidal infection, manifested in this case by apical bronchiectasis.

## COMMENT AND SUMMARY

The thirteen cases reported here illustrate the striking ability of the body to arrest coccidioidal infection despite destructive lesions and evidence of a long existent pathologic condition. This power of arrestment, both in human beings and in animals, has been described by Cox and Smith.[10] They reported 4 necropsies, during which they found fibrocaseous and calcified foci in lungs and hilar lymph nodes which contained spherules of C. immitis. They also observed that in one third of a group of rats inoculated with small measured numbers of spherules the resultant lesions were calcified five months or more after inoculation. In certain of the animals spherules were found deeply embedded in fibrous foci two years after inoculation.

10. Cox, A. J., and Smith, C. E.: Arrested Pulmonary Coccidioidal Granuloma, Arch. Path. **27**:717 (April) 1939.

Pulmonary coccidioidal cavities, such as occurred in 12 cases reported here, are characterized by quiescent roentgenographic appearance and innocuous behavior. They form easily visible localizations of primary coccidioidal infection in the lung. The concept of cavity development has been well reviewed by Eloesser.[11] Besides stating his own observations and conclusions, he cited the experimental work of Moolten and the theory of Reinders. According to these authors, cavitation arises from an initial small necrotic focus which produces an interruption of the unyielding pulmonary framework of the lung parenchyma. Then, because of the interplay of several factors, including elastic retraction of the surrounding resilient lung, partial bronchial obstruction and marginal atelectasis of the surrounding alveolar tissue, there results a ballooning out of the small caseonecrotic focus, which gradually assumes the proportions of a cavity. In coccidioidal infection, lack of considerable tissue destruction and peripheral inflammatory reaction produces a thin-walled structure which has somewhat the appearance of a solitary cyst. Bronchial communications may be small or large, single or multiple, and they determine whether such a cavity may be filled through the bronchial tree by radiopaque substances, such as iodized poppyseed oil. These communications also determine whether the cavity will resist closure after collapse therapy. Such cavities are to be considered as more or less benign, stabilized structures which are the end results of a small focus of destruction produced by the primary coccidioidal infection. It is conceivable that they may disappear spontaneously if bronchial occlusion becomes total and permanent. Primary infection may also become a deep-seated localized infection of the bronchial wall, eventually producing a small area of bronchiectatic change associated with destruction and sacculation of the bronchial wall, as illustrated by case 13.

With ever increasing recognition of cases of coccidioidal infection outside of California, it is important to focus attention on the pulmonary aspects of the disease, especially cavitation. Primary coccidioidomycosis occurs much more frequently than does coccidioidal granuloma, and the pulmonary cavitation, likewise, is almost exclusively associated with the primary infection, rather than with the granuloma stage. Confusion with pulmonary tuberculosis, which is closely simulated in roentgenographic appearance, must be avoided. Pulmonary cavitation associated with primary coccidioidomycosis is relatively benign as compared with the lethal cavitation occurring in tuberculosis. Prognosis is therefore decidedly favorable, and treatment should be conservative. Apparently it is not at all essential to apply the rigid code of treatment

11. Eloesser, L.: Blocked Cavities in Pulmonary Tuberculosis, J. Thoracic Surg. **7**:2 (Oct.) 1937.

used in tuberculosis and to close the cavity by whatever means becomes necessary. From the standpoint of public health, it is not necessary to isolate the patient or to separate him long from his usual mode of living and employment. Persistent pulmonary hemorrhage or the occasional large cavity associated with spherule-laden sputum may be an indication for pneumothorax.

Careful study and observation of the 13 cases reported here form the basis for these deductions. The first case is an instance of failure to differentiate early between coccidioidal cavitation and tuberculous cavitation and thereby to protect the patient from prolonged institutional care, excessive treatment and the temporary stigma of a diagnosis of tuberculosis. Marking the pitfalls to be avoided is one of the prime purposes of this paper. In addition, attention is directed to the occurrence of a characteristic "latent" type of pulmonary cavitation in association with, or residual to, primary coccidioidomycosis. Criteria for diagnosis are outlined and the frequent occurrence of hemoptysis described. One case of apical coccidioidal bronchiectasis is also included.

Dr. C. E. Smith, Miss R. J. Wheatlake and the staff of the Department of Public Health, Stanford University School of Medicine, performed the bacteriologic studies. I was also assisted by Dr. Clara Hughes and Miss Frieda Ward, of the Tulare-Kings Counties Joint Tuberculosis Hospital.

# PROGNOSTIC VALUE OF VARIOUS CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF ACUTE MYOCARDIAL INFARCTION

## II. ULTIMATE PROGNOSIS

SAMUEL A. LEVINE, M.D.
BOSTON
AND
FRANCIS F. ROSENBAUM, M.D.
ANN ARBOR, MICH.

In recent years there has been a growing appreciation of the fact that not only do patients recover from acute myocardial infarction but often they can return to a reasonably normal way of life for some years. In his report in 1912, Herrick [1] pointed out that myocardial infarction was not necessarily fatal. However, for the next fifteen years, emphasis was placed on the clinical and the electrocardiographic diagnosis of this disease, and not until recently was attention directed to the course of those patients who survived an acute episode. Interest was no doubt stimulated by isolated reports [2] of persons who lived long and active lives after recovering from an acute attack. In this connection, it is interesting to note that Ryle [3] inferred, from Sir Everard Home's accounts, that John Hunter lived for twenty years after a typical acute coronary occlusion. However, as Levine [4] and Levy [5] pointed out, the prognosis in cases of coronary arterial disease remains extremely difficult. It seemed worth while to us to analyze the various clinical and electrocardiographic features of a large number of patients who had

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912.

2. Thayer, W. S.: Reflections on Angina Pectoris with Special Regard to Prognosis and Treatment, Internat. Clin. **1**:1, 1923. White, P. D.: Longevity After Coronary Thrombosis, J. A. M. A. **100**:233 (Jan. 28) 1933. Lewis, W. H.: Coronary Occlusion: A Report of Unusual Activities After Recovery, ibid. **114**: 484 (Feb. 10) 1940.

3. Ryle, J. A.: A Note on John Hunter's Cardiac Infarct, Lancet **1**:332 (Feb. 18) 1928.

4. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Baltimore, Williams & Wilkins Company, 1929.

5. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936, chap. 8.

recovered from what was, so far as could be determined, their first myocardial infarction, in order to discover, if possible, any clues which might lead to a more accurate prediction of the future course of the disease.

## METHOD AND MATERIAL

A study was made of 372 patients, all of whom had been seen and followed in consultation practice by one of us (S. A. L.). It was felt that these patients represented a broad cross section of those who had recovered from their initial myocardial infarction, for some had had an attack requiring hospitalization, others had been treated at home and still others had been ambulatory throughout the acute episode. The exact number of subsequent attacks of coronary thrombosis was not ascertained. Of the entire group, 101 patients were followed to the time of death (average, forty-one and one-tenth months). The follow-up period for the remainder averaged twenty-seven and six-tenths months; 60 per cent of them were followed for thirteen months or more.

According to the electrocardiographic findings at the time of the acute attack or the first examination thereafter, the patients were classified into six groups based on the presence of (1) anterior infarction (145), (2) posterior infarction (110), (3) bundle branch block (14), (4) partial and (or) complete heart block (11), (5) low voltage of the QRS complex in the standard leads, with no other significant abnormality (22) and (6) defective intraventricular conduction (15). A seventh, unclassified group included those patients whose electrocardiograms showed only minor or bizarre changes (54). In addition there was 1 patient in whom occurred the electrocardiographic changes which have been described by Wood, Wolferth and Bellet [6] as indicative of an infarction of the lateral wall of the left ventricle. For one half of all the patients electrocardiograms taken either during the acute episode or during the first month after the onset of symptoms were available for review. For the others, it was necessary that the demonstrable changes be unequivocal in order for a patient to be included in one of the first six groups just listed. The unclassified group consisted particularly of patients seen some weeks or months after the acute attack, and for most of them (78 per cent) serial electrocardiograms were not available.

## DURATION OF SURVIVAL

The duration of life following the initial attack of acute coronary thrombosis has been variously reported. Bedford [7] found the average to be six months in 31 cases but indicated that some persons might live more than five years. Wilson [8] suggested that most patients die within two years. White [9] reported an average survival period of three years

6. Wood, F. C.; Wolferth, C. C., and Bellet, S.: Infarction of the Lateral Wall of the Left Ventricle: Electrocardiographic Characteristics, Am. Heart J. **16**:387 (Oct.) 1938.

7. Bedford, D. E.: Prognosis in Coronary Thrombosis, Lancet **1**:223 (Jan. 26) 1935.

8. Wilson, T. E., in discussion on Clark, L. J.: Prognosis in Coronary Disease, New Orleans M. & S. J. **86**:365 (Dec.) 1933.

9. White, P. D.: The Prognosis in Angina Pectoris and Coronary Thrombosis, J. A. M. A. **87**:1525 (Nov. 6) 1926.

in 18 cases of coronary thrombosis which he selected from 160 cases of angina pectoris described by Mackenzie. For 80 patients followed by White and Bland [10] the average was one and nine-tenths years, but there were 94 additional patients in their series who were still living after an average of three and two-tenths years. For the 101 patients in this study who were followed to the time of death, the average length of life after the initial attack of myocardial infarction was forty-one and one-tenth months (table 1). It was almost the same for 44 patients who had anterior infarctions (forty-two and six-tenths months) as for 27 patients who had posterior lesions (forty and nine-tenths months). Eleven patients who showed only a low voltage of the QRS complex in the standard leads lived an average of thirty-eight and three-tenths months, whereas 12 patients with electrocardiograms which we termed "unclassified" had the longest average survival, fifty-one months. For

TABLE 1.—*Duration of Survival After Acute Myocardial Infarction*

| Electrocardiographic Group | Number of Patients | Average Survival Period, Months |
|---|---|---|
| Anterior infarction | 44 | 42.6 |
| Posterior infarction | 27 | 40.9 |
| Bundle branch block | 2 | 4.0 |
| Partial and complete heart block | 3 | 15.3 |
| Defective intraventricular conduction | 2 | 44.5 |
| Low voltage QRS in standard leads | 11 | 38.3 |
| Unclassified | 12 | 51.0 |
| Total | 101 | 41.1 |

2 patients with bundle branch block, 3 with partial and (or) complete heart block and 2 with defective intraventricular conduction the average period of survival was four, fifteen and three-tenths and forty-four and five-tenths months, respectively.

Of the entire group of 101 patients known to have died, 27 per cent succumbed within one year, 47 per cent within two years and 73 per cent within five years. Four patients died ten years or more after the initial attack. The longest period of survival was twelve years, that of a man aged 36 who suffered a severe attack requiring hospitalization and yet on recovery was able to return to full activity as a traveling salesman for many years.

There were 271 patients who were still living at the time of the last follow-up information. The average period of survival for this group

10. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis: A Study of Five Hundred Cases of the Former Condition and of Two Hundred Cases of the Latter, Am. Heart J. **7**:1 (Oct.) 1931.

was twenty-seven and six-tenths months. One hundred and seven patients (40 per cent) had been followed for one year or less, 58 (21 per cent) for thirteen to twenty-four months, 70 (26 per cent) for twenty-five to sixty months and 32 (12 per cent) for five to ten years. There were 4 patients (1 per cent) who were followed more than ten years. This last group included 1 man who had a definite myocardial infarction at the age of 57 but was still working and active twenty-five years later, with an occasional pill of glyceryl trinitrate for anginal pain.

At first glance it might appear that if the living patients were followed until the final outcome, the average survival period would be lengthened. From previous experience with similar problems this has not appeared to be the case when the end result for a significant number of patients is known. It must be borne in mind that among those that are still living there are a good many who have so far survived only a few months and are likely to die within a year or two, thus counterbalancing some that have survived for more than ten years. We, therefore, are of the opinion that the average figure of forty-one and one-tenth months, as given previously, is valid. This is in accord with results of an earlier study,[11] in which the survival after the first attack of coronary thrombosis of patients with angina pectoris was found to be between three and three and five-tenths years.

### SUBSEQUENT ANGINA PECTORIS

Results of previous studies regarding the occurrence of angina pectoris following recovery from acute coronary thrombosis show a rather wide variation, possibly due to the fact that no differentiation was made between those patients suffering initial attacks and those with recurrent episodes. Willius[12] found that 45 per cent of his patients experienced subsequent angina. Hochrein and Schneyer[13] reported it in 26 per cent of their patients who recovered. Padilla and Cossio[14] stated that six months after the attack 5 per cent of their patients suffered from angina pectoris.

In this series angina pectoris was present some time after the attack in 63 per cent of all the patients. The interval between the attack

11. Eppinger, E. C., and Levine, S. A.: Angina Pectoris: Some Clinical Considerations with Special Reference to Prognosis, Arch. Int. Med. **53**:120 (Jan.) 1934.

12. Willius, F. A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**:1890 (May 30) 1936.

13. Hochrein, M., and Schneyer, K.: Das Schicksal des Myocardinfarktes, Ztschr. f. Kreislaufforsch. **28**:257 (April 15) 1936.

14. Padilla, T., and Cossio, P.: Pronostico del infarto de miocardio, Rev. argent. de cardiol. **1**:181 (July-Aug.) 1934.

and the appearance of angina was variable. In some persons it persisted throughout the acute episode and into convalescence, without remissions. In others the cardiac pain did not make its appearance for several years after the initial episode. This symptom was found to develop with equal frequency in each of the various electrocardiographic groups, except that it was somewhat more common in the unclassified group and less common in the one characterized by a low voltage of the QRS complex in the standard leads. Furthermore, the average severity of the angina, when it did make its appearance, was approximately the same throughout the various electrocardiographic groups, if it was classified on a scale of absent, mild, moderate, marked and severe, depending on the degree of activity required to bring on distress. In addition, it was seen that for 25 patients who died without experiencing subsequent angina pectoris, the average duration of survival was the same (forty-three months) as it was for 67 patients known to have

TABLE 2.—*Relation of Age at Time of Initial Attack to Duration of Survival*

| Age, Year | Number of Patients | Average Survival Period, Months |
|---|---|---|
| 30-39 | 5 | 63.0 |
| 40-49 | 24 | 54.8 |
| 50-59 | 36 | 37.6 |
| 60-69 | 30 | 29.9 |
| 70-79 | 4* | 43.5 |

* One patient in this age group survived one hundred and thirty-eight months.

manifested this symptom at some time before death (forty-three and one-tenth months). It would appear, therefore, that on the whole the electrographic pattern at the time of the initial myocardial infarction does not permit, of itself, a prediction regarding the presence or absence of subsequent angina pectoris, nor does the development of this symptom at some time after the recovery make possible any estimate regarding the length of life which may be expected.

### SUBSEQUENT CONGESTIVE HEART FAILURE

Padilla and Cossio [14] found that 9 per cent of their patients had congestive failure six months after the acute attack. Of the 169 patients whom Willius [12] followed, 3.6 per cent became bedridden because of congestive failure. In our series there were 364 patients for whom there was definite information regarding subsequent decompensation. Their conditions were classified as one of five degrees: absent, mild, moderate, marked and severe. In 72 per cent of the total series heart failure was absent, in 19 per cent it was mild or moderate and in 9 per cent it was marked or severe. When only those patients who were known to have died were considered, there were 57 per cent who showed

no evidence of decompensation up to the time of the final illness, 18 per cent who had mild or moderate congestive failure and 25 per cent in whom the failure was marked or severe.

A similar analysis of each electrocardiographic group indicated that the average degree of subsequent congestive failure was somewhat greater in those patients whose original lesion was anterior than in those in whom it was posterior. This is in accord with the impression expressed by Wood and his associates [15] that recovery of cardiac function was more rapid and complete after posterior than after anterior infarction. Some evidence of congestive failure appeared in 35 per cent of patients with an anterior lesion and in 14 per cent of those with a posterior infarct. In the groups who showed bundle branch block, defective intraventricular conduction or low voltage the incidence was 49 per cent.

A further check of the patients who were known to have died revealed that those who showed no evidence of congestive failure up to the time of the terminal event had an average survival period of forty-five and seven-tenths months, as compared with that of thirty-six and eight-tenths months for those who had shown some signs of decompensation.

It may be concluded, therefore, that after the initial attack of myocardial infarction some evidence of congestive failure develops in slightly less than one-half the patients before they die and that those in whom heart failure appears tend to have a shorter life span. Furthermore, decompensation occurs somewhat more frequently after anterior than after posterior infarction.

### RECOVERY OF ACTIVITY

Previous investigations regarding ability to resume activity after recovery from an acute coronary thrombosis have each yielded practically the same results. Conner and Holt [16] reported that 86 per cent of their patients were essentially well after six months, 42 per cent after three years and 21 per cent after five years. Of the patients followed by Cooksey,[17] 78.1 per cent were restored to their previous occupation. Willius [12] found that 75.7 per cent were restored to good health or were well with restrictions. More recently Master and Dack [18] have pointed

15. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observation on the Use of Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933.

16. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, Am. Heart J. **5**:705 (Aug.) 1930.

17. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Especial Reference to Prognosis, J. A. M. A. **104**:2063 (June 8) 1935.

18. Master, A. M., and Dack, S.: Rehabilitation Following Acute Coronary Artery Occlusion, J. A. M. A. **115**:828 (Sept. 7) 1940.

out that 59 per cent of their patients were able to return to work after the first attack.

In this series information regarding the subsequent degree of activity was available for 354 patients. The capacity of each was classified as one of four degrees: essentially full activity, slightly restricted activity, moderately restricted activity and complete incapacitation. It was found that 30 per cent of all patients were able to return to work and to full duty at least for an appreciable length of time, 45 per cent to partial activity and 22 per cent to moderately restricted activity. Only 3 per cent were completely incapacitated. In this analysis we have considered the state of activity maintained for some months after the first attack. This obviously would be altered by secondary attacks or progressive myocardial impairment as time went on. Although the effect of subsequent attacks was not studied in detail, it did appear, as Master and Dack have indicated, that the degree of recovery grew progressively less with each bout of acute myocardial infarction.

The degree of recovery in patients with anterior infarction was slightly less than in those with a posterior lesion, 72 per cent of the former returning to full or partial duty, as compared with 86 per cent of the latter. Patients who had electrocardiograms showing partial and (or) complete heart block or only low voltage of the QRS complex suffered a greater than average degree of subsequent restriction.

It appears, then, that three fourths of the patients who recover from their first attack of acute coronary thrombosis are able to resume full or partial activity and that a greater number of those with posterior infarction are able to do so than of those whose electrocardiograms indicate another type of lesion.

### SEX

As in most large series of cases of acute myocardial infarction, there was a striking predominance of men (89 per cent of 372 patients). In an earlier but less extensive study [4] it was also suspected that women were not apt to remain in as good health for as long a time as men. However, White and Bland [10] and Padilla and Cossio [14] reported that sex was unimportant in the prognosis of coronary thrombosis. This has not been true in the present analysis. For 89 men followed to the time of death the average survival was forty-four and two-tenths months, whereas for 12 women known to have died the average survival after the initial myocardial infarction was eighteen and three-tenths months. It might be said that this discrepancy is accounted for by the fact that the male patients include all those who were between the ages of 30 and 40 at the time of their first attack and that, as will be pointed out, patients of such age have a longer subsequent expectancy. However, after excluding all who fell into this age group at the onset, we found

that the average survival period for men was forty-three and one-tenth months, a value still definitely above that for women. Of the women known to have died, none lived more than five years. Two of the 30 women still living at the time of the last follow-up observation indicate that occasionally a long survival can occur; 1 woman was still fairly active after nearly fifteen years, and the other had lived nine years.

In the determinations of the frequency and degree of angina pectoris experienced subsequent to recovery in the two sexes, it seemed that the averages for men and for women were nearly the same. In general, this held true irrespective of the electrocardiographic pattern, with the possible exception that the small groups of women who had an anterior

TABLE 3.—*Comparison of Blood Pressures Before and After Acute Myocardial Infarction*

| Before Attack | | Few Months After Attack | | Last Blood Pressure Recorded (One to Several Years After Attack) | |
|---|---|---|---|---|---|
| Systolic | Diastolic | Systolic | Diastolic | Systolic | Diastolic |
| 170 | 110 (½)* | 170 | 100 (13)* | 180 | 90 (32)* |
| 185 | 90 (13) | 140 | 80 (7) | 170 | 80 (32) |
| 240 | 120 (¾) | 140 | 80 (8) | 180 | 70 (19) |
| 210† | 145 (¾) | 200 | 150 (4) | 210 | 140 (12) |
| 100 | 90 (2) | 140 | 85 (11) | 180 | 120 (14) |
| 180† | 90 (6) | 140 | 90 (2) | 190 | 95 (25) |
| 160† | 100 (¾) | 130 | 80 (2) | 155 | 80 (13) |
| 140 | 80 (10) | 120 | 60 (2) | 155 | 85 (36) |
| 180† | 110 (¾) | 155 | 100 (2) | 155 | 110 (10) |
| 192† | 125 (¾) | 142 | 94 (2) | 150 | 98 (24) |
| 162† | 95 (5) | 130 | 80 (4) | 130 | 78 (12) |
| 160 | 100 (24) | 140 | 100 (19) | 150 | 90 (31) |
| 200 | 100 (22) | 160 | 90 (4) | 200 | 100 (6) |
| 156 | 82 (11) | 148 | 110 (2) | 148 | 92 (6) |
| 210 | 160 (5) | 210 | 140 (4) | 185 | 140 (7) |
| 210† | 115 (¾) | 210 | 130 (1) | 232 | 138 (36) |
| Average 182 | 107 | 156 | 96 | 173 | 100 |

* Numbers in parentheses indicate time in months before or after attack.
† In this case blood pressure readings were known within a few weeks or months before the attack and during the subsequent months and years.

lesion, partial and (or) complete block or defective intraventricular conduction had somewhat more severe angina than men who showed the same type of tracing with their acute attacks.

On the other hand, it was found that the average degree of congestive failure which appeared after recovery from an initial myocardial infarction was definitely greater in women than in men. Of the former 72 per cent had no or only mild decompensation while for men the corresponding figure was 86 per cent. This feature was especially noticeable if the infarction originally present was located posteriorly or if the electrocardiograms had shown bundle branch block, auriculoventricular block or a low voltage of the QRS complex in the standard leads. The greater frequency of heart failure among women may well be accounted for by the greater prevalence of hypertension.

Master and Dack [18] have reported that sex was not a factor in influencing return to work. However, the average degree of recovery of activity was definitely greater in men than in women in this series. This was further brought out by the evidence that 79 per cent of the men were able to return to full or partial activity whereas only 51 per cent of the women had that degree of recovery of function. Here, again, this variation held true no matter what the electrocardiographic pattern may have been, with the exception of those patients with tracings of the unclassified type. In that group the average degree of recovery was equal for the two sexes.

It may be said, therefore, that after recovery from an initial myocardial infarction women, as compared with men, tend to live a shorter time, have more congestive failure and are less able to return to a useful degree of activity.

AGE

In regard to age statistics, study of this series of patients yielded much the same results as would a study of any large group of persons with initial acute coronary thrombosis. The average age at the time of the attack for all patients was 53.9 years. The average age of the men was 53.3 years and of the women 58.9 years. Of the women, 86 per cent were 50 years of age or over, as contrasted with 65 per cent of the men. Twenty patients (5 per cent), all men, were in the decade from 30 to 39.

The frequency and severity of subsequent angina pectoris were determined for patients in each decade. It was found that the average severity of subsequent cardiac pain was less in the 30 to 39 year age group than in the 40 to 49 and 50 to 59 year age groups, but was approximately the same as that experienced by patients over the age of 60. In addition, 80 per cent of the patients who made up the 30 to 39 year age group had no or mild subsequent angina pectoris, as compared with 69 per cent of all other patients.

The frequency and the severity of subsequent congestive failure were determined for patients in each decade. It appeared that, in general, the average degree of subsequent heart failure rose progressively with the age at the onset of the attack. Of those patients in the decade 30 to 39, 85 per cent had no subsequent heart failure, whereas corresponding results for the other age groups were 75 per cent for the decade 40 to 59 and 62 per cent for the decade 60 to 79.

Cooksey [17] reported that younger persons were more regularly able to resume a fuller share of previous activity after recovery than were older patients. Master and Dack [18] also found this to be the case and expressed the belief that the age of the patient was the most important factor in determining return to work. Our analysis has yielded a

similar result. The average degree of recovery of activity grew progressively smaller with advancing age, and the number of those able to return to work became less and less with each decade. Of the patients who were between 30 and 39 years old, 65 per cent returned to full duty, as contrasted with 39 per cent of those between 40 and 49, 26 per cent of those between 50 and 59 and 29 per cent of those who were 60 or older.

White and Bland [10] expressed the opinion that young patients lived longer, as a rule, after suffering an acute coronary thrombosis. This belief was later supported by observations of Glendy, Levine and White.[19] In their study of patients with angina pectoris, Eppinger and Levine [11] found that those whose symptoms began before the age of 50 lived two and three-tenths years longer than those whose pain first appeared after that age. On the other hand, Padilla and Cossio [14] concluded that age made no difference in the prognosis. In this study we have analyzed the group of patients who were known to have died to determine the influence of the age at the time of the attack on the subsequent duration of survival. It was evident that the younger patients lived longer than the older ones (table 2). Five patients who were between 30 and 39 years of age lived an average of sixty-three months. For 24 patients who were in the 40 to 49 year decade the average subsequent life span was fifty-four and eight-tenths months. For 36 patients between 50 and 59 years old it was thirty-seven and six-tenths months, while for 30 patients in the 60 to 69 year age group it was twenty-nine and nine-tenths months. There were 4 patients in the 70 to 79 year decade with an average survival of forty-three and five-tenths months; this figure would have been much lower but for a 72 year old man who lived one hundred and thirty-eight months after his attack.

In summary, it is clear that after recovery from acute coronary thrombosis younger patients have less subsequent angina or congestive heart failure and as a rule live longer and more useful lives than do older patients.

### SEVERITY OF ORIGINAL ATTACK

It seemed worth while to determine whether the severity of the manifestations during the initial acute myocardial infarction offered any indication regarding the course that followed recovery. For each patient the gravity of the acute episode was classified as mild, moderate, severe or extremely severe. In this classification, various features, such as severity and duration of pain, amount of dyspnea, degree of shock and

19. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth: Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, J. A. M. A. **109**:1175 (Nov. 27) 1937.

evidence of pulmonary congestion, were evaluated. It was seen that the average severity of the initial attack was the same for each of the electrocardiographic groups. On the whole, this was true as well for each age group.

The severity of the original episode bore little relation to the subsequent angina pectoris which patients in the various groups experienced, inasmuch as the average degree of subsequent cardiac pain was the same in those with mild attacks as in those whose attacks were considered severe. The only significant variation here was that the patients with a severe attack in conjunction with anterior infarction tended to have more intense angina pectoris afterward than those with an original episode of the same degree resulting from a posterior lesion.

The severity of the manifestations of the original acute coronary thrombosis did bear some relation to the subsequent degree of congestive failure, however, for the more severe the initial bout the greater the later decompensation tended to be. In addition, this observation held generally true in each of the electrocardiographic groups. This relation was valid as well when an analysis was made of the degree of subsequent recovery of activity in each of the four classified groups. It was seen that the patients who had mild or moderate attacks were able to resume a greater degree of activity than those who had severe or extremely severe attacks. This was true whether the infarction was located anteriorly or posteriorly. However, in those with bundle branch block or heart block the subsequent limitation of activity was great no matter how severe the original episode.

Willius [12] expressed the opinion that there was no correlation between the duration of the pain with the attack and the duration of survival. Utilizing the survival periods for those patients who were known to have died, we observed that for 11 patients with mild attacks the average survival was thirty-five and eight-tenths months, for 69 patients with moderate attacks forty-three and eight-tenths months and for 18 patients with severe attacks thirty-five and two-tenths months, while 2 patients who had extremely severe attacks died after an average period of twenty-eight months. In individual cases this absence of any close correlation was even more striking, for frequently patients with mild attacks died within two or three months while others with severe attacks lived as long as twelve years.

From the foregoing data it follows that the severity of the acute attack bears no significant relation to the degree of subsequent angina or the duration of survival. There is a greater incidence of congestive failure and physical disability in those with the more severe initial episodes.

COMPLICATIONS OF ATTACK

There were 16 patients of the entire series who were known to have shown transient auricular fibrillation at the time of the acute attack. It was interesting to analyze the subsequent course of their disease. The average degree of subsequent angina pectoris experienced by these patients was definitely less than the average for all. The average degree of subsequent congestive failure for this number was higher than for those who showed no fibrillation. The average degree of recovery of activity for this group was slightly less than that for all the patients. There were 6 patients with transient auricular fibrillation who were followed to the time of death. Their average length of life was sixty-four and five-tenths months. In addition, for the 10 patients who were still living at the time of the last follow-up information, the average survival period was forty-one and two-tenths months. Although the number of patients is small, the results suggest strongly that those who have transient auricular fibrillation with the initial myocardial infarction have less subsequent angina pectoris, slightly more congestive failure and physical incapacitation and the same, or an even longer, duration of life than patients who do not show this arrhythmia.

In 29 patients of the total of 372, a pericardial friction rub was heard during the acute illness. Of this number, 17 had an anterior infarct, 7 had a posterior lesion, 1 showed bundle branch block, 2 had low voltage of the QRS complex and 2 fell into the unclassified group. So far as subsequent angina pectoris is concerned, these patients were no different from all others. There was a tendency for them to have more congestive failure, however, 66 per cent having no or mild decompensation, as compared with 86 per cent for all others. Moreover, only 64 per cent of these patients returned to full or partial activity, as compared with 76 per cent for all others. Thirteen who showed pericardial friction with the initial attack were followed to the time of death. Their average survival period was forty-one and one-tenth months, exactly the same as that for all other patients. It may be said, then, that the appearance of a pericardial friction rub during the acute phase may possibly point to a greater degree of heart failure and a lesser degree of resumption of activity after recovery, but that it does not otherwise influence the subsequent course.

Four patients were known to have had paroxysmal ventricular tachycardia at the time of the acute attack. Although they were few, their subsequent course did not differ greatly from the average, and of the 2 known to have died the survival periods were three and ninety-seven months, respectively. The last observation indicates that the development of this arrhythmia during an acute infarction is not incompatible with a reasonably long and useful survival period. In 4

patients who showed mental disturbances during the acute phases of their disease the subsequent course was no different than that in the majority of other patients. Three of them were able to return to partial work and were still living after two years. The fourth was completely incapacitated and died after three months. It was our experience that if a fairly satisfactory recovery of cardiac function resulted, any psychosis which might have been present entirely disappeared.

### PREVIOUS ANGINA PECTORIS

Previous reports concerning the incidence of angina pectoris prior to acute coronary occlusion have yielded results ranging from 22.4 [12] to approximately 50 per cent.[20] Adequate information regarding the presence or absence of previous cardiac pain was available for 288 patients in this series. Of the total, 38 per cent had definite previous angina pectoris, 10 per cent had noted atypical distress prior to the attack and 52 per cent gave no history of antecedent cardiac pain.

Conner and Holt [16] found that in 22 cases there were 8 in which the pain ceased after the attack, 5 in which it was worse, 2 in which it was less and 7 in which there was no change. Willius [13] reported that although the incidence of subsequent angina in his patients was 45.1 per cent, it was only 32.4 per cent in those who had not had distress prior to the attack. The review of this series has shown somewhat similar results. The average severity of subsequent angina pectoris in those who gave a history of definite or probable previous angina was greater than in those who had noted no antecedent pain. Furthermore, of the former patients only 22 per cent had no subsequent angina, whereas of those who had no previous pain, 44 per cent also had none after recovery. As a corollary, it may be said that in 37 per cent of the entire series angina pectoris first appeared after recovery from acute myocardial infarction. It also was found that the average degree of subsequent congestive failure and limitation of activity was greater for those who gave a history of angina prior to the initial acute coronary thrombosis.

White and Bland [10] have stated that the previous occurrence or duration of angina pectoris does not affect the prognosis of coronary thrombosis. In this series data regarding previous angina pectoris were available for 70 of the patients followed to the time of death. For 34 patients with typical previous distress, the average period of survival was thirty-six and two-tenths months. Six patients with atypical

20. Smith, F. M.; Rathe, H. W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, J. A. M. A. **105**:2 (July 6) 1935. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**: 4 (Jan. 7) 1928.

antecedent pain had an average survival period of fifty-seven and eight-tenths months. The average subsequent life span of 30 patients who had no angina prior to the initial episode was thirty-eight and six-tenths months.

These results indicate, therefore, that patients who have angina pectoris prior to their initial myocardial infarction have more subsequent cardiac pain and congestive failure and a lesser degree of recovery of activity. However, although they are somewhat more uncomfortable and less active, their period of survival is not particularly shorter than that of patients who have been free of pain prior to their infarction.

### CHANGES IN BLOOD PRESSURE

It has been generally recognized that a fall in blood pressure is a common accompaniment of an acute myocardial infarction. This lowering of the pressure is usually found to persist during the early weeks of illness, while the patient is still in bed. It is possibly this fact which has given rise to the feeling that the blood pressure is commonly lowered permanently. In fact, it has been observed that frequently the blood pressure is decidedly lower for some months after recovery has taken place, even when the patient is ambulatory and fairly active.[21] Little attention has been given to the ultimate changes in the blood pressure observed after following such patients for long periods.

Among those patients analyzed in part 1 of this study,[22] there were 16 for whom blood pressure readings taken before the attack and those taken some months or years after recovery had taken place (table 3) were available. For 7 of them, the readings were known within a few weeks to not more than a few months before the attack and throughout a period of months to years thereafter. The average determinations for the entire group of 16 and those for the smaller but more detailed subgroup of 7 followed an almost identical pattern. The levels before the attack in the group and the subgroup, respectively, were 182 and 185 systolic and 107 and 110 diastolic. A few months after the attack the corresponding averages were 156 and 158 and 98 and 103. A year or more later they were 173 and 175 and 100 and 107. There were, however, distinct variations among the different patients, so that in some the pressure returned to approximately the original state within a few

21. Levine, S. A.: Cases of Coronary Occlusion with Recovery, M. Clin. North America **8**:1719 (May) 1925. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: Circulatory Dynamics in Myocardial Infarction, Arch. Int. Med. **54**:997 (Dec.) 1934.

22. Rosenbaum, F. F., and Levine, S. A.: Prognostic Value of Various Clinical and Electrocardiographic Features in Acute Myocardial Infarction: I. Immediate Prognosis, Arch. Int. Med. **68**:913 (Nov.) 1941.

weeks whereas in others it did so only after some months, or occasionally a year or two. In fact, it is not infrequently observed that the pressure after a temporary fall may rise to the previous levels during the early days after the onset of the acute myocardial infarction. It is of some interest that in only 3 of the 16 patients was the systolic blood pressure 30 mm. or more lower a year or two after the attack than it had been before. The conclusion may be drawn from this analysis that after a temporary fall in pressure there is a tendency over the following months for a gradual return to approximately the original level.

### MODE OF DEATH

Willius [12] reported that of 201 patients with coronary thrombosis, 191 died of causes related to the heart, whereas 10 died of causes unrelated to the heart. Hochrein and Schneyer [13] have also studied this problem, with results of the same order as those in our analysis. Of the 101 patients known to have died, information regarding the nature of the terminal event was available for 80. Of this number 32 (40 per cent) died as a result of a subsequent attack of myocardial infarction, 28 (35 per cent) died suddenly and unexpectedly and 16 (20 per cent) died of congestive heart failure. There were only 4 patients (5 per cent) who died of causes unrelated to the heart, 1 of mesenteric thrombosis, 1 of a bronchogenic carcinoma, 1 of a renal neoplasm and the last as the result of a peculiar, undiagnosed febrile illness.

### SUMMARY AND CONCLUSION

A study was made of 372 patients who had recovered from an initial attack of acute myocardial infarction, in order to determine the type of progress that might be expected and to see whether any predictions as to prognosis could be made from the various clinical and electrocardiographic features.

*Duration of Survival.*—The average period of survival of 101 patients known to have died was forty-one and one-tenth months. There was a negligible difference in the length of survival between patients with anterior and those with posterior infarction (forty-two and six-tenths and forty and nine-tenths months, respectively). The survival period for those showing QRS complexes of low voltage was thirty-eight and three-tenths months, while in the group with electrocardiograms called unclassified (showing minor alterations in the ventricular complex) it was fifty-one months.

Of 101 patients known to have died, approximately one-fourth succumbed within one year, one-half within the first two years and three-fourths within the first five years. The remainder died after

varying intervals, which ranged from five to twelve years. One of the living patients was still carrying on twenty-five years after the initial attack.

*Subsequent Angina Pectoris.*—Sixty-three per cent of all patients manifested angina pectoris some time after the initial attack of myocardial infarction. The onset of this symptom varied from the early days of the acute illness to years after recovery. There were only slight variations in the incidence and severity of this complaint in the various electrocardiographic groups. The presence or absence of subsequent angina did not influence the period of survival.

*Subsequent Congestive Failure.*—Only 28 per cent of all patients had subsequent congestive heart failure; in 19 per cent it was mild or moderate, and in 9 per cent it was marked or severe. When only those known to have died are considered, the incidence of decompensation was greater (43 per cent). The frequency of heart failure was distinctly greater with anterior infarction (35 per cent) than with a posterior lesion (14 per cent). It was greater still in the groups showing bundle branch block, defective intraventricular conduction and low voltage (49 per cent). The average survival periods with and without heart failure were thirty-six and eight-tenths and forty-five and seven-tenths months, respectively.

*Recovery of Activity.*—The subsequent degree of physical activity was known for 354 patients. Thirty per cent returned to essentially full duty, 45 per cent to partial activity and 22 per cent to moderately restricted activity for an appreciable length of time before a further major setback occurred. In this regard patients with an anterior lesion did less well than those with a posterior lesion. Patients with heart block or curves of low voltage were particularly limited.

*Sex.*—The average survival period for men was forty-four and two-tenths months and for women eighteen and three-tenths months. The occurrence of subsequent angina was essentially the same for the two sexes. Congestive failure and limitation of physical activity were distinctly greater in women.

*Age.*—The average age for men was 53.3 years and for women 58.9 years. The severity of subsequent angina was found to be less in those under 40 and over 60 than in those between these two ages. The degree of congestive failure and physical disability rose progressively with advancing years. The younger patients had a distinctly longer survival period than the older ones. The average progressively decreased from sixty-three months for those under 40 years of age to about thirty months for those over 60 years of age.

*Severity of Original Attack.*—The severity of the initial attack of acute coronary thrombosis was not a measure of the degree of sub-

sequent angina or the duration of survival. The more severe initial episodes were followed by a greater incidence of congestive failure and physical disability.

*Auricular Fibrillation.*—The follow-up study of 16 patients who showed transient auricular fibrillation during the acute attack indicated that they seemed to have less subsequent angina pectoris, slightly more congestive failure but about the same duration of survival as those who did not show this arrhythmia.

*Pericardial Friction Rub.*—The 29 patients who had pericardial friction with the initial attack displayed no more angina, tended to have slightly more congestive failure and were slightly more incapacitated than were those who did not manifest this sign, but the patients had the same survival period.

*Other Complications.*—The few patients who recovered after having paroxysmal ventricular tachycardia or a psychosis with the acute attack did about as well as the average for the entire series.

*Previous Angina Pectoris.*—The presence of angina pectoris before the attack of acute myocardial infarction rendered patients more likely to have subsequent angina, decompensation and limitation of activity but did not shorten the survival period.

*Blood Pressure.*—For 16 patients there were data concerning the blood pressure shortly before, several months after and one or more years after the attack of acute myocardial infarction. The averages for the three readings were 182, 156 and 173 systolic and 107, 98 and 100 diastolic, respectively. There were individual variations, so that in some the pressure returned to approximately the original level very quickly and in others only after a year or two.

*Mode of Death.*—Of the 80 patients for whom the mode of death was known, 40 per cent died of a subsequent attack of myocardial infarction, 35 per cent died suddenly, 20 per cent died of congestive failure and only 5 per cent died of a cause unrelated to the heart.

*Conclusion.*—It may be stated that, although the course that follows an acute myocardial infarction varies a great deal, there are some clinical features analyzed in this study which may aid materially in judging the prognosis.

# Progress in Internal Medicine

## REVIEW OF NEUROPSYCHIATRY FOR 1941

STANLEY COBB, M.D.
BOSTON

### WAR NEUROSES

Before 1915 neurosis was a disorder respected and studied by some specialists in neuropsychiatry but belittled by most physicians as something "imaginary" or "weak." Their attitude toward this ill often smacked of the moralistic; the patient "ought to snap out of it" if he "only had the guts." The patients, too, sometimes felt that their troubles were not medical, but moral or spiritual, and kept away from psychiatrists because they did not want to admit to themselves and others that there was anything wrong with their "minds."

All this was greatly changed by the war experience. Severe neurotic symptoms soon began to appear among officers and men. At first they were explained as "shell shock," the implication being that there was concussion of the central nervous system. This explanation was found to be wrong except in a small number of cases. Three to 9 per cent of all casualties were recognized as psychogenic. In the American Expeditionary Force the total was about 33,000. In England in 1921, pensions were being given to 65,000 veterans for psychogenic disorders (exclusive of some 32,000 with cardiac neuroses).

All this has greatly altered the attitude of members of the medical profession toward neurosis. In the first place, these symptoms often appeared in men who were considered brave and strong; excellent officers were often affected. The moralistic attitude was manifestly nonsensical. As time went on the psychologic mechanisms concerned in some cases became obvious to a large number of medical officers. They had the personal experience of seeing how emotional stress would precipitate stupor, tremors, blindness, deafness, paralyses, fits, fugues and cardiac, respiratory, gastrointestinal and genitourinary symptoms. This experience caused a remarkable advance in psychiatry during the years following the war. Now another war is on, and the same problem is cropping up in new and old forms.

Realization of the importance of organizing the knowledge of the past experiences and learning quickly from the new has resulted in

the appearance of several important reviews and papers. Miller [1] has edited a book on "The Neuroses in War," made up of well coordinated chapters by a number of experienced Englishmen. Zabriskie and Brush [2] have done a fine piece of work in a 35 page review of "Psychoneuroses in War Time." Kardiner [3] has written a long monograph on "The Traumatic Neuroses of War." Besides these three long contributions, there are a number of shorter recent papers telling of the current experiences of this war,[4] which differ from experiences of earlier wars principally in the fact that civil populations are now also exposed to the horrors of bombing, machine gun fire and incendiarism.

To one who has looked through hundreds of pages of this interesting, but somewhat discursive and repetitive, material, the impossibility of an accurate review is obvious. One can, however, put down what seems to be the consensus and the more advanced ideas.

*Etiology.*—Heredity plays a part only in that some men are born with more sensitive nervous systems than others. If the strain imposed on an average, sound soldier is severe enough, he can break. The earlier existence of neurotic symptoms in civil life predisposes to their reappearance under stress of war, and a lesser stress than would be needed to break a sounder man may well throw a predisposed soldier into neurotic reactions. Of course, because of past experiences and individual conditioning, strain to one man is not strain to another, at least not to the same degree. The main common denominator is the internal conflict of the soldier between the instinct of self preservation and the social urge to carry on: fear versus duty. Other common conflicts are with discipline, dirt and killing. In some persons with much "repressed aggression" killing may lead to great anxiety and complete invalidism. It seems that their whole carefully built up education against cruelty breaks down and gives them insight into what cruelties they might perform if let loose. This they recognize as entirely incompatible with the personal integration they have achieved, and the conflict becomes unbearable.

---

1. Miller, E.: The Neuroses in War, New York, The Macmillan Company, 1940.

2. Zabriskie, E. G., and Brush, A. L.: Psychoneuroses in War Time, Psychosom. Med. **3**:295-329, 1941.

3. Kardiner, A.: The Traumatic Neuroses of War, Psychosomatic Medicine Monograph II-III, New York, Paul B. Hoeber, Inc., 1941.

4. (*a*) Culpin, M.: A Week-End with the War Neuroses, Lancet **2**:257, 1940. (*b*) Debenham, G.; Sargant, W.; Hill, D., and Slater, E.: Treatment of War Neurosis, ibid. **1**:107, 1941. (*c*) Slater, E., and Sargant, W.: Acute War Neuroses, ibid. **2**:1, 1940. (*d*) Wittkower, E., and Spillane, J. P.: Neuroses in War: Part I, Brit. M. J. **1**:223, 1940. (*e*) Wittkower, E., and Spillane, J. P.: Neuroses in War: Part II, ibid. **1**:265, 1940.

Fatigue, poor diet, sleeplessness and illness may all lead to a state of exhaustion that predisposes to psychogenic troubles. The main sources of strain are danger of death, guilt over killing, responsibility, separation from family and sexual deprivation. It has been found that the type of man most likely to break down is the unsociable fellow who is self centered and overconscientious.

*Clinical Picture.*—This is too complex and varied to describe in brief. Almost any symptom may appear. The commonest categories are the rather simple conversion hysterias (found mostly among enlisted men) and the difficult anxiety states (found more often among officers). Here should be mentioned the "effort syndrome" (soldiers' heart, "D. A. H."); it seems probable that these three terms are synonyms for "anxiety neurosis"; so the total psychoneurotic casualties of the British and American armies in the last war ought probably to be increased by some 20,000 or 30,000 officially classed as "cardiovascular." In the light of present knowledge these are almost certainly disorders of the autonomic nervous system, expressed by fatigability, breathlessness, palpitation, precordial pain, dizziness, blurred vision, sweating and vasomotor disturbances.

The prodromal signs are important. Men likely to break down can often be recognized beforehand by complaints of fatigue, increased use of alcohol and tobacco, irritability, unsociability, dulness, crying spells and sweating.

The new thing in this war seems to be the greater number of cases in which mental confusion and stupor form the center of the clinical picture. Some men, especially those seen after the evacuation of Dunkerque,[4c] showed extreme exhaustion and tension; they had tremor and such tense muscles in limbs and face that they were sometimes thought to have paralysis agitans. A great number of psychosomatic syndromes are also being recognized. This is probably not a new situation but a new point of view that admits the possibility of psychologic causes behind gastrointestinal, genitourinary, cutaneous, intestinal and cardiac symptoms. Gastric ulcer is a great problem at present.

*Prevention.*—It is, of course, important to prevent the nervously unfit from entering the armed forces, probably even more so in the navy than in the army. This can be done only by proper examination of recruits by men who know how to elicit and evaluate a history of neurosis. It is also important to have the draft board examiners realize that the government is now paying pensions to thousands of psychoneurotic veterans who should never have been let into the army. The attitude is too common that a man who is willing to tell of nervous symptoms is malingering and that the army "will do him good." The

fact is that he will do the army no good, and even if he is malingering, the army certainly does not want him.

In the routine of army life it is important to have proper periods for rest and recreation. Of course war is the most stressful phenomenon known and this cannot be modified, but whenever possible periods of tension should be shortened. Also, recreation should be such as to give the men satisfaction; amusements are not enough and often lead to disgust and depression. All this is in the sphere of the morale officer. The medical officer, however, may perform an important prophylactic function by talking to officers and men on the physiology of fear. One might as well admit frankly that every one is afraid of death and that the symptoms are universal. It is better to have the men recognize this than to add to their natural fear reaction the worry over symptoms. Many a man has thought he might be going to drop dead of heart disease because he had palpitation, and many others have mistaken emotional diarrhea for "cholera morbus."

*Treatment.*—There is great unanimity among the various authors in urging early and adequate treatment. If the patient can be seen by a psychiatrist within thirty-six hours of the onset of severe symptoms, the likelihood of quick recovery is greatly increased. Full diet and forcing of fluids are usually important, for exhaustion and dehydration have often been mistaken for severe neurosis. Narcosis is used freely. This is probably necessary in smaller hospitals, but in base hospitals hydrotherapy should be available. Sometimes the aforementioned regimen, with long hours of sleep, induced by barbiturates if necessary, will largely clear up the symptoms.

In most cases, however, psychotherapy is also needed. If the patient is in good rapport he can immediately be given a chance to talk over his fears. If this is not enough, and if explanation does not relieve him, hypnosis or intoxication with amytal, pentothal or evipal may be necessary to aid the patient to recall and relive the dreadful experiences which are upsetting him.[5] Alcohol or light anesthesia may be used, but the standard technic is the administration of 7½ grains (0.5 Gm.) of sodium amytal intravenously. This is given slowly, so that the patient at first becomes euphoric and loquacious, perhaps telling of important repressed experiences and often, then and there, overcoming motor or sensory symptoms. Later he sleeps and may awake relieved. Hypnosis is sometimes useful early in patients with hysterical conversion symptoms.

If these emergency methods do not work immediately the psychiatrist must begin with more prolonged methods, such as those employed in

5. Miller,[1] appendix D.

civil practice. Psychoanalysis is impossible under war conditions, but the knowledge of human reactions attained by a sound psychoanalytic training can be of great use in applying shorter forms of psychotherapy. The important thing is for the physician to obtain a sympathetic rapport with the patient, so that he can go into the traumatic episode and clear up the amnesias step by step. Reeducation and occupation are important. Back-slapping reassurance, persuasion and exhortation are as useless as the discarded ordeals of faradic pain too popular in the last war.

### ELECTRIC SHOCK THERAPY FOR PSYCHOSES

The use of electricity in neurology and psychiatry is over one hundred years old, but the delivery of strong electric shock to the brain is a relatively new procedure. Bini,[6] in 1938, used such treatment in Italy. He took up "electroshock" because he wished to cause convulsions without the disagreeable and traumatic effects often accompanying metrazol fits. In this he seems to have had some success. The method was taken up on the Continent and in England, and later in the United States. Gonda[7] reviews the literature in a recent paper and describes the method and the results. To my mind he paints too rosy a picture and minimizes the risks. The convulsions are severe and may cause fractures. The picture is usually as follows: When the switch is thrown, the patient is apparently knocked unconscious and goes into an instantaneous muscular spasm like that of an animal whose motor cortex has been strongly stimulated. There is then an interval of a few seconds before the convulsion proper starts. The patient turns pale, the pupils dilate and the eyes deviate upward. Then, with a cry, the patient goes into extensor spasm, arching the back and holding a rigid posture. Breathing stops and the patient grows cyanotic. Then the spasm is interrupted, so that clonic jerks become more and more frequent and severe. After thirty to sixty seconds the convulsive movements cease and the patient lies limp. Three or four minutes later the patient begins to make aimless movements and look about in a confused way; for five to ten minutes more he may remain semiconscious and may behave as if terrified. The confused period may end with sudden awakening and a surprised expression, or the patient may remain somewhat confused for hours. Apparently the amnesia caused by suddenly being knocked unconscious is both retrograde and antigrade, for the patient has no unpleasant memory of the experience. On the whole the fits are more severe than clinical grand mal.

6. Bini, L.: Experimental Researches on Epileptic Attacks Induced by Electric Current, Am. J. Psychiat. **94**:172, 1938.

7. Gonda, V. E.: Treatment of Mental Disorders with Electrically Induced Convulsions, Dis. Nerv. System **2**:84, 1941.

Such an episode would seem to me severe enough to require hospitalization. With this some electrotherapeutists [8] do not agree, believing that the procedure may be applied to outpatients if several hours are allotted for preparation and observation after the shock.

Just what takes place in the brain as a result of these electric shocks is not known. The histologic effect of electric currents of various kinds and strengths has of course been studied,[9] but studies on animals with currents comparable to those used for therapeutic shocks are few and poorly reported. Some of the workers briefly state that animal work was done and showed no lesions. Such reports are not convincing because sufficient data are not given about number of animals, histologic technic and controls. Recent work by Alpers and Hughes [10] is carefully reported: A group of 15 cats, each of which had ten threshold shocks (i. e., just enough to cause convulsion) showed ten subarachnoid hemorrhages and eight cerebral hemorrhages. Another group of 15 cats in a more prolonged experiment showed four hemorrhages and four chronic cerebral lesions. Heilbrunn and Liebert [11] took biopsy specimens from the brains of rabbits at short intervals for several hours after electric shock. All the early specimens showed changes in the nerve cells, but one and a half hours after the shock many cells had returned to normal. This is important evidence but should be amplified. Added to this is the electroencephalographic evidence of damage to the brain lasting for weeks or months. Grinker, Levy and Serota [12] found abnormal waves developing after electric shock in 5 of 12 patients; these 5 and 3 more also showed mental disturbances in which the higher intellectual functions were conspicuously affected; i. e., the patients showed a "slap happy" state of euphoria. Both the clinical psychologic disturbances and the abnormal brain waves were at their worst in the first weeks after shock and gradually improved, indicating reversible lesions, like those described in the biopsy experiments on rabbits. Sufficiently long observations, however, have not been made to say whether or not

8. Myerson, A.: Experience with Electric-Shock Therapy in Mental Disease, New England J. Med. **224**:1081, 1941.

9. Morrison, L. R.; Weeks, A., and Cobb, S.: Histopathology of Different Types of Electric Shock on Mammalian Brains, J. Indust. Hyg. **12**:324, 1930. Weeks, A. W., and Alexander, L.: Distribution of Electric Current in Animal Body: Experimental Investigation of Sixty Cycle Alternating Current, J. Indust. Hyg. & Toxicol. **21**:517, 1939.

10. Alpers, B., and Hughes, J.: The Brain Changes in Electrically Induced Convulsions in Cats, Arch. Neurol. & Psychiat., to be published.

11. Heilbrunn, G., and Liebert, E.: Biopsies on the Brain Following Artificially Produced Convulsions, Arch. Neurol. & Psychiat. **46**:548 (Sept.) 1941.

12. Grinker, R. R.; Levy, N. A., and Serota, H. M.: Electroencephalographic and Clinical Studies Following Metrazol and Electrically Induced Convulsive Therapy of Affective Disorders, Arch. Neurol. & Psychiat. **46**:542 (Sept.) 1941.

any permanent disorder remains. A few cases are coming to notice in which epilepsy seems to have been started. Probably an electroencephalogram should be made in each case before shock treatment to rule out latent or "subclinical" epilepsy.

My own opinion is that a convulsion is an extremely severe symptom and always indicates cerebral injury whether it is "spontaneous" or is "therapeutically" induced. I believe that electric shock is less dangerous than metrazol but is to be classified as one of the destructive forms of therapy. As a physician who believes that good therapy consists in conserving rather than injuring the organism, I look with alarm at the rapid spread of electric shock therapy and believe that it should be tried out for a year or two longer by careful workers trained in physics and electrophysiology, before the shocking machines are put into the hands of therapeutists not so trained. The psychiatrist who cares for patients during prolonged depressions has great responsibility and a wearisome and often thankless task; so the temptation to do something and try something new is often great. The question is whether such treatments are justified.

So far the results in states of depression are encouraging. In schizophrenia and neurosis they are poor. Gonda [7] reports 11 patients with depression, 10 of whom recovered. Of his 29 schizophrenic patients, 17 showed "complete remission" and 6 improved. It is important to note however, that these patients were in the early stage of the disease, most of them with symptoms of less than a year's duration. The remission rate for such patients in the smaller hospitals with adequate staff and equipment—using no shock therapy, is practically as high. Myerson [8] shows clearly that depressive states are the ones most benefited by electric shock. Of his 24 depressed patients 17 showed remission or marked improvement. None of his 9 schizophrenic patients was significantly benefited, nor were 3 patients with chronic neurosis.

At the meeting of the American Psychiatric Association at Richmond, Va., in June 1941, eight hospitals combined their results and gave a demonstration to show that electroshock therapy had advantages over other radical procedures, being more acceptable to the patient, easier to administer by the physican, productive of fewer fractures (5 per cent) and less expensive. Standard electric shocks given to animals were found to cause hemorrhages in the cortex and the arachnoid. The therapeutic results can be tabulated as follows:

| Condition | Number of Patients | | | |
|---|---|---|---|---|
| | Treated | Recovered | Improved | Not Improved |
| Involutional melancholia | 76 | 55 | 14 | 7 |
| Manic-depressive, manic | 29 | 16 | 5 | 8 |
| Manic-depressive, depressed | 106 | 79 | 11 | 16 |
| Schizophrenia | 119 | 25 | 31 | 63 |

In evaluating these figures it must be remembered that most manic-depressive patients recover spontaneously and many of those with early schizophrenia have remissions. The remarkable and hopeful data are those in the cases of involutional melancholia.

As I just indicated, my objections to electroshock therapy are not against the method per se. The results show that it has some value. My fear is that the method is spreading too rapidly, that accidents may occur and that damage may be done to many brains before psychiatrists are aware of the risks. Already the commercial aspect is becoming prominent, and many machines are on the market. Some of these are not reliable, and some of the salesmen make the method seem ridiculously simple. Well trained electrical engineers have been astonished at the magnitude of the shocks given and at the faulty machines used; for example, some therapeutists rely on apparatus with inaccurate timing and erroneous measurement of current. One physicist who has looked into the matter reports that the commercial machines seem to be at fault in one or more of the following ways:

(*a*) The timer depends either on the properties of electronic circuits or on various kinds of "time delay" relays. These methods are not adequate for timing very short intervals (tenth seconds). To be thoroughly reliable the timer should consist of a mechanical switching mechanism driven by a synchronous motor of ample power.

(*b*) Current regulation is attempted indirectly by applying a regulated voltage to a supposedly known resistance. Actually the skull does not represent a simple ohmic resistance but is complicated by capacitive and polarization effects. Furthermore, there may be a difference of several hundred per cent between the resistance as measured immediately before the treatment and the resistance that obtains during the brief interval the current is passing through the skull and brain. In short, it is *not* possible to regulate the dosage (current) by regulating the applied voltage. What is needed is a device that will regulate current directly, independent of resistance. Measuring the resistance is then not necessary so far as the treatment current is concerned, but it is nevertheless advisable to do so just before giving the shock, to make sure that all the connections in the circuit, including those on the scalp, are in good contact.

(*c*) Current flow during the shock treatment is supposed to be measured on some machines by ordinary ammeters. This is impossible during the brief shocks used, and many of the data published concerning amperage of current administered to patients are therefore worthless. Brief currents can be measured by some form of recording oscillograph. However, an alternative method is to make the current flow

first through a "dummy" patient, when it can be measured at leisure with an ammeter, and then transfer it without change to the patient for a brief interval. This method has the important advantage that the current is known before the treatment.

(*d*) Using current regulation (as indicated in *b*), rather than voltage regulation, requires some form of control to prevent excessive voltage from ever developing across the output terminals in case of faulty connections.

A shock therapy apparatus embodying these principles ought to give reliable data and should be safe, in the sense that the time and current dose may be adjusted beforehand with the assurance that the patient will receive just this intended dose. Guillemin [13] has designed an apparatus of this type, now in use at the McLean Hospital, Belmont, Mass.

### APHASIA

During recent years Ingham, Nielsen and von Hagen, in Los Angeles, have taken an especial interest in aphasia and have collected and carefully studied a large number of cases. These have been frequently reported in the *Bulletin of the Los Angeles Neurological Society* and have resulted in two longer contributions by Nielsen [14] which are a great aid to the neurologist in understanding disturbances of language and allied disorders of cerebral function. No short summary of these disorders can be adequate and accurate because they comprise the difficult field where neurology meets psychiatry and physiology is taken over by psychology. In short, integration reaches a state of such complexity that neural impulses arouse meaningful and symbolic reactions. The levels of reflex and racial reactions are surpassed, and learned skills that are cerebrally localized in a leading hemisphere are attained. Among these skills is language.

Nielsen's contribution lies in organizing the classic data of such authorities as Jackson, Henschen, Goldstein and Foerster and in adding to these data new cases which fill in the gaps in evidence and explain the discrepancies. The crucial new facts have come from the neurosurgeons and their observations on the effects of cerebral lobectomy and stimulation.

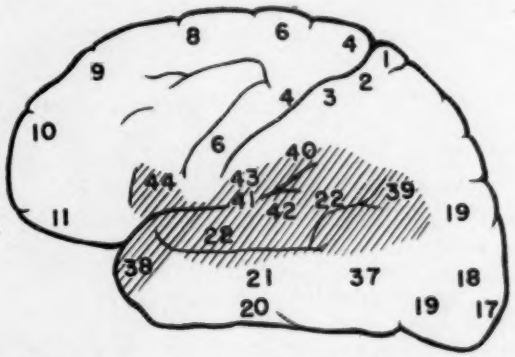
The senses important to language are vision and hearing (sense of touch replaces vision for blind people reading Braille, but it is secondary for normal people). The two main senses each have three levels of

13. Guillemin, V.: Personal communication to the author.

14. Nielsen, J. M.: A Textbook of Clinical Neurology, New York, Paul B. Hoeber, Inc., 1941; Agnosia, Apraxia, Aphasia, Los Angeles, Los Angeles Neurological Society, 1936.

integration. Visual perception is localized in area 17 (fig.), visual recognition in area 18 and revisualization in parts of area 19. A lesion at the first level causes blindness at the second, loss of recognition (the patient does not know what the perceived object means; hence he has visual agnosia). A lesion in area 19 causes loss of power to revisualize scenes or persons. The patient cannot remember the plan of a house and cannot get home even though he may recognize the street or house he is seeing at the moment. He is visually disoriented because he cannot bring back series of pictures.

The auditory sense has three levels, not so clearly defined. The first level is not in the cortex; primary auditory perception is in the mesial geniculate bodies of the thalami. Each cochlea sends fibers to both geniculate bodies. Thence fibers go to the temporal lobes, where




A diagram of the left cerebral hemisphere showing the location of histologically recognizable areas (after Brodmann). The shaded zone includes areas involved in language. Areas 4 and 41 lie largely in the depths of the fissures.

cortical areas 41 and 42 make the center for auditory recognition (level 2). Since the innervation is bilateral, a single cerebral lesion cannot cause complete agnosia, and even bilateral lesions never cause deafness. Acoustic agnosia for sounds is not known to occur without acoustic verbal agnosia, but in many cases of the latter the recognition for sounds is retained. For example, a patient may have lost his knowledge of the meaning of word symbols but can still recognize a whistle, the sound of crumpling paper, etc., and say what is going on. Thus it is obvious that the acoustic mechanism is more concentrated in space in each temporal lobe but has less unilaterality in the dominant hemisphere than is the case with the visual mechanism.

Recognition of learned symbols has been mentioned in respect to words heard; for words seen the center is in the angular gyrus, area 39,

and a lesion here causes visual verbal agnosia, or "word blindness," as opposed to the "word deafness" resulting from a lesion in the temporal lobe.

So much for a brief description of the most important points concerning the receiving end of linguistic disorder, the "sensory aphasia" of older authors. The motor side is equally complex and depends on an understanding of the fact that no learned motor skill can be practiced without an ideational plan. This is a psychic elaboration necessary as a precursor to the carrying out of any complex motor act. This ideational planning is called eupraxia; the normal person knows how to do a thing quickly and almost automatically when requested. A defect of such performance in response to command is apraxia. It is a symptom of injury to the sensorimotor elaboration areas of the cortex, corresponding to agnosia from a lesion in the more strictly sensory area. In relation to most performances eupraxia is bilateral, the acts of one hand, for example, being planned in the opposite precentral and supramarginal gyri. Lesions of these areas (parts of 6 and 40) or their fiber connections may cause apraxia.

Apraxia of the organs of speech (tongue, lips, larynx) causes "motor aphasia"; the patient loses the memory of how to make the movements to articulate words; he may know just what he wants to say, but he cannot get the plan of the word into his mind. A lesion of Broca's area (44) causes this symptom. Much controversy once raged over "Broca's aphasia," but Nielsen's summarizing of the data, including that from modern surgical procedures, leaves no doubt that motor aphasia has this precise localization. The cases that seemed to disprove it are probably cases in which area 44 of the minor side took over the function of motor speech readily; i. e., the patients were somewhat ambidextrous. Moreover, expletive speech is always possible with the minor side; only propositional speech is lost when the major area 44 is injured. In other words, the function of language is largely concentrated in the leading hemisphere, but a primitive sort of speech (emotional, expletive, habitual) is subserved in the homologous areas of the minor hemisphere. Areas 39, 44, 19, 18 and 17 are the most unilateral in function, in that order. Areas 41 and 42 are less unilateral. Individual variation in relation to the degree of handedness is important.

The last point, of the many good ones emphasized by Nielsen, to which I wish to call attention is the following: Area 39 has the function of symbolic visual recognition, i. e., understanding letters and words by sight. Because words were first learned by hearing, however, area 39 cannot function if cut off from areas 41 and 42. During the process of learning to read, words are sounded out or told to one. Thus the portion of the temporal lobe lying between areas 39 and 42 is of great

importance. This takes in the posterior part of area 22 and the upper part of area 37. A lesion here may cause as much loss of reading ability (alexia) as a lesion directly in area 39. Moreover, because language is learned by associating vision and hearing with objects and symbols, this area is particularly important. In fact, Nielsen calls it "the language formation area."

Take, for example, the case of objective nouns, the simplest and commonest words used. They are names, usually of objects seen. So engrams must be stored in areas 22 and 37 correlating both visual and auditory meanings. That this is true is shown by cases of temporal lobectomy in which the language formation area of the leading hemisphere is removed. The result is amnesic aphasia. The patient has lost the storage mechanism for nouns; his "naming center" is gone. When shown a pen, he uses circumlocution and may reply "It's to write with" but cannot say "pen." He is suffering from the symptom of anomia, one of the commonest subdivisions of aphasia. It is, in a way, the opposite of motor aphasia.

If one takes these main symptoms (which are well explained physiologically), agnosia, motor aphasia and anomia, and adds the obvious complications, it is seen that many special sorts of aphasia are possible. But by sticking to the principles laid down, these strange phenomena can largely be explained and localized. For example, one can hear music as well as words; therefore "amusia" is found. One can learn several languages and have marked aphasia in one but little in another. Symbols used for mathematics are different from letters; so one may have agnosia for figures. In fact, loss of the ability to calculate is found after lesions in various areas and is not well understood. Semantic aphasia, a term coined by Head, should be mentioned because it is the commonest of all aphasias and is not localizable. It consists of a quantitative reduction in the capacity for and comprehension of speech. The victim has a little of all language functions left but cannot put sentences together or express any complex idea. This phenomenon is present in persons with diffuse cerebral lesions commonly senile, in toxic patients and in normal but excessively fatigued persons. In fact, almost all patients with aphasia have an element of the semantic form, and careful examination will usually show some mental loss. Semantic aphasia is a form of dementia.

The complexity of the subject of aphasia, apraxia and agnosia (symbolization) is remarkable but fascinating. Many volumes have been written on it, and many physicians shun the study of language because it seems hopelessly complicated. One is grateful to Nielsen for a reasonable simplification.

Any mention of aphasia brings to mind the name of Henry Head. He was one of the leading neurologists of this generation; born on Aug. 5, 1861, he had long training both in England and in Europe. His leadership in the medical world was indicated by his holding the editorship of *Brain* from 1905 to 1922. During the first World War he was especially interested in the effects of injuries of the brain and wrote a monograph on aphasia which was the result of many years' study and follow-up observation of these war wounds. He died on Oct. 9, 1940, after suffering for almost eighteen years with slowly progressive paralysis agitans. He was a man of broad interests, many accomplishments and much fortitude.

### THE NEUROLOGIC APPROACH TO MENTAL DISORDER

In his presidental address to the Section of Psychiatry of the Royal Society of Medicine in March 1941, Symonds [15] spoke on the subject used as a heading for these paragraphs. His logic is so sound and his examples so well chosen that I wish to express my enthusiasm for his point of view and give one quotation. During recent years there has been too much specializing, and specializing within specialties. In neuropsychiatry this has led to the practice of psychotherapy by persons who know nothing of the brain. Psychiatry has been narrowly defined by some as the study of interpersonal relationships. Others consider that "organic neurology" can be separated from psychiatry and psychology. In regard to "medical psychology" (in this country the psychotherapy practiced by clinical psychologists), Symonds says:

> The medical psychologist also asserts that for his purpose training in neurology is unnecessary. He may be prepared to admit that all mental activity has its physical basis, and that brain is the organ of mind, but these propositions are, for him, of theoretical value only. They have no real bearing upon the practical diagnosis and treatment of the neuroses. An approach to these problems in terms of neurophysiology and neuropathology may be an interesting intellectual exercise, but has no practical significance. I have already attempted to indicate the fallacies in such argument, with especial reference to the affective disorders. I would take as another example the diagnosis and treatment of neurosis following head injury. Here we have a patient whose adjustments to inner need and external stimulus are faulty. How far is this due to inherited disposition, training, experience, present needs and difficulties; how far to the nature and situation of cerebral damage? Is the cerebral injury of reversible or irreversible character? If there is headache, how much is due to meningeal adhesion, alterations in the cerebrospinal fluid pressure or circulation, or disordered cortical rhythm? How much to fear, depression, or defeatism arising from difficulty in coping with the situation as a whole? If there is insomnia, how much is due to anxiety, how much to hypothalamic damage? I submit that the answers to some of these questions are impossible without

15. Symonds, C.: The Neurological Approach to Mental Disorder, Proc. Roy. Soc. Med. **34**:289, 1941.

neurological training, and that unless they are all answered diagnosis and treatment must be at fault. I do not think this is an unfair example. There are many other instances in which knowledge of cerebral function in health and disease in relation to nutrition—including vitamin supply, effect of drugs, endocrine disorder, or oxygen need—is essential to the proper understanding and treatment of neurosis. . . .

Looking to the past I believe that neurology and psychiatry in this country were kept apart at first, because the neurologist was interested in morbid anatomy, and the psychiatrist in the care of the insane. . . . At present the gap is narrower than it has ever been. The fruits of recent research and experiment have emphasized common interest, for example the work of Bard and others on hypothalamic function, the contribution of the biochemists to the understanding of brain metabolism, the study of cortical rhythm by the electro-encephalogram, the lessons of continuous narcosis and convulsive therapy. Looking to the future I believe that the merging of the two specialties into one is not only desirable but inevitable.

# Book Reviews

**The Modern Treatment of Syphilis.** By J. E. Moore, M.D., Associate Professor of Medicine, the Johns Hopkins University, with the collaboration of J. E. Kemp, M.D.; H. Eagle, M.D.; P. Padget, M.D., and M. S. Goodwin, M.D. Second edition. Price, $7. Pp. XII + 674, with 98 figures and 122 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The first edition of this book appeared in 1933. The reviews which it received are worth mentioning for they are so remarkably uncomplaining. The *Archives of Dermatology and Syphilology* (**30**:330 [Aug.] 1934) called the book a great one and a real contribution to the knowledge of syphilis. *The Journal of the American Medical Association* (**102**:1328 [April 21] 1934) termed it a classic and prophesied many future editions. The ARCHIVES (**53**:632 [April] 1934), so likely to be conservative and uneffusive, fairly outdid itself: "From time to time books appear which start out as landmarks in a subject so far as they rid themselves of the deadwood of tradition and by a consideration of actual facts formulate definitely a new point of view. Such a result, in our opinion, has been achieved by Moore in his discussion of the modern treatment of syphilis."

The second edition is 139 pages longer than the first edition and is not only more ample but better in every way. It is up to date; it is better illustrated; the tabulations are easier to understand; the language continues readable and easy to follow, and the bibliography has grown as a clever gardener allows a hedge to grow—by a wise combination of pruning and fresh planting. Thus the bibliography is not much longer than it was but a good deal broader by virtue of useful additions and wise deletions. There are two entirely new chapters which add to the effectiveness of the volume as a whole, one on the public health aspects of syphilis and the other dealing with the matter of intensive arsenic therapy.

The book is sure to be successful. Successful books, like successful doctors, are worth cultivating. Medical students and physicians are advised to introduce themselves to this book at once in order to become thoroughly acquainted with the modern treatment of an old and important disease.

**Preeclamptic and Eclamptic Toxemia of Pregnancy.** By Lewis Dexter and Soma Weiss. Pp. 415, with 44 figures. Boston: Little, Brown & Co., 1941.

No subject in medicine has been in a greater state of confusion than the "toxemias of pregnancy," encrusted by traditions often of almost medieval antiquity and studied for the most part by men not trained in the proper methods. Real light seems now to have come from the careful studies of Dexter and Weiss. Here, for the first time, the reviewer finds a really intelligible and satisfying account of these puzzling disorders, made possible mainly by the training of the authors in vascular and renal disease. Clinical features, pathophysiologic aspects and anatomic lesions are all correlated, and each chapter is followed by liberal bibliography. Useful charts illustrate the case reports.

**The Essentials of Occupational Diseases.** By Jewett V. Reed and A. K. Harcourt. Price, $4.50. Pp. 225, octavo. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This book seems admirably designed to orient the physician in the essentials of occupational disease. A long list of chemical poisons and their effects, concisely discussed in alphabetic order, is followed by material on physical agents, the cutaneous lesions of occupational disease, silicosis, malignant disease associated with occupation and, finally, occupational disease due to infection. A well selected bibliography covers 10 pages.

# INDEX TO VOLUME 68

Book Reviews are grouped together and are indexed under that heading in alphabetical order under the letter B.


**Abdomen**: See also Gastrointestinal Tract
cause of so-called side ache that occurs in normal persons; personal observations, 94
Abnormalities and Deformities: See under names of organs and regions, as Ribs; etc.
Abscess: See under names of organs and regions
Acacia: See Nephritis
Acetone: See Blood, ketone bodies
Acidosis, efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
Acrocyanosis: See Cyanosis
Acromegaly and diabetes, 148
Acropachyderma: See Extremities
Acrosclerosis: See Scleroderma
Addison's Disease, abnormal function of kidney in, 984
carbohydrate metabolism in, 991
changes in body fluids in, 985
diagnosis of, 1000
diseases of adrenal glands, 979
electrolyte metabolism, 981
pathology of, 980
treatment of, 1004
Adrenal Preparations, adrenal cortical substances, 997
adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
Adrenals; adrenal cortical hyperplasia, 1019
diseases of adrenal glands; Addison's disease, 979
diseases of adrenal glands; tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances, 1010
diseases of adrenal medulla, 1032
medullary hyperadrenalism, 1037
tumors of adrenal cortex, 1010
Age, Old: See Old Age
Ainhum, 621
Air, sterilization of, 367
Air Passages: See Respiratory Tract
Air Raids, shelter legs, 622
Allergy: See Anaphylaxis and Allergy
Altschule, M. D.: Acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
Amputation, 658
Amylase in Blood: See under Blood
Amyloidosis, hepatic function in patients with, 309
Anaphylaxis and Allergy, immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
Andrus, W. DeW.: Differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
Anemia, acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
Anemia—Continued
"primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
Anesthesia, paravertebral block, 636
Aneurysm, 644
Angioma, tumors of blood and lymph vessels, 615
Animals, unusual infections contracted from animals, 360
Aphasia, 1240
Appendicitis; review of literature, 821
Arteries: See also Aneurysm; Arteriosclerosis; Blood pressure; Blood, vessels; Embolism; Periarteritis; Thrombosis; etc.
inflammation; arteritis, 615
multiple fresh coronary occlusions in patients with antecedent shock, 181
oscillometry, 610
Arteriosclerosis, 610
primary pulmonary vascular sclerosis, 560
Arteritis: See Arteries, inflammation
Arthritis, 354
and circulation, 617
serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18

**Bacilli**: See Bacteria
Bacillus Friedländeri: See Bacteria, mucosus capsulatus group
Bacteremia, significance of bacteremia caused by Staphylococcus aureus; study of 122 cases and review of literature concerned with experimental infection in animals, 851
Bacteria: See also Staphylococci; Streptococci; Viruses; etc.
abortus and melitense group; brucellosis, 351
abortus and melitense group; chemotherapy of bacillary infection, 333
infection caused by Bacillus violaceus, 353
mucosus capsulatus group; Friedländer pneumonia, 348
Shigella: See Dysentery
Tularense: See Tularemia
Bacteriophage, 367
Bancroft, P. M.: Elliptic erythrocytes in man, 1043
Bashour, J. T.: Chemical factors in formation of gallstones, 1037
Bauman, E.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
Bauman, L.: Chemical factors in formation of gallstones, 1037
Bennett, R. H.: Treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
Berk, J. E.: Diagnosis of carcinoma of pancreas, 525
Bilden, E.: Determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
Biliary Tract: See Gallbladder; Liver
Binger, M. W.: Acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513

Block, W. D.: Serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
Blood: See also Erythrocytes; Leukocytes
acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
Circulation: See also Arteries; Capillaries; Heart; Veins; etc.
circulation and arthritis, 617
coagulation; differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
direct cultivation of Bacterium tularense from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
Diseases: See Anemia; etc.
fats and lipoids; serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
fusospirochetosis; recovery of causative organisms from blood with report of 2 cases, 80
ketone bodies; origin from fats and their regulation, 674
origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
picture in chickenpox, 294
pigment; acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
pressure, abnormalities of, 625
pressure; exercise test, 622
pressure, high; adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
pressure, high; state of motor centers in circulatory insufficiency, 498
pressure, high; studies on "essential" hypertension; association of hypertension with organic renal disease, 261
pressure, high; surgical treatment of hypertension, 653
pressure, low; hypotension, 635
pressure studies on West Indians and Panamanians living on Isthmus of Panama, 466
response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
sugar in case of complete hypophysectomy, 893
sugar; metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
sugar; metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
Vessels: See also Arteries; Capillaries; Periarteritis; Veins; etc.
vessels; vasospastic disorders, 619
Blumgart, H. L.: Multiple fresh coronary occlusions in patients with antecedent shock, 181
Body Fluids: See Fluids
Bones, acropachyderma with pachyperiostitis; report of case, 687

Book Reviews:
Age Morphology of Primary Tubercles; H. Sweaney, 180
Annual Review of Physiology; J. M. Luck and V. E. Hall, 374
Book Reviews—Continued
Avitaminoses; W. H. Eddy and G. Dolldorf, 850
Bacillary and Rickettsial Infections; W. H. Holmes, 177
Biologie der Grossstadt; B. de Rudder and F. Linke, 180
Biology of Laboratory Mouse; edited by G. D. Snell, 373
Cardiac Clinics; F. A. Willius, 1041
Cardiologia (Cardiology); J. M. Hoyos, 179
Clinical Immunology, Biotherapy and Chemotherapy in Diagnosis, Prevention and Treatment of Disease; J. A. Kolmer and L. Tuft, 1040
Clinical Pellagra; S. Harris, 370
Diabetic Manual; E. P. Joslin, 662
Dietetics for Clinician; M. A. Bridges, 850
Diseases of Digestive System; S. A. Portis, 371
Diseases of Nails; V. Pardo-Castello, 1041
Doctor and Difficult Child; W. Moodie, 372
Electrocardiography in Practice; A. Graybiel and P. D. White, 371
Enfermedades del riñon (Diseases of Kidneys); J. M. Hoyos, 370
Essentials of Occupational Diseases; J. V. Reed and A. K. Harcourt, 1246
Frank Howard Lahey: Birthday Volume by various authors and sponsors, 371
Handbook of Communicable Diseases; F. H. Top and others, 1041
Hemorrhagic Diseases; K. K. Nygaard, 178
Herzkrankheiten: I. Physiologie, Beurteilung und funktionelle Pathologie des Herzens; M. Hochrein, 186
Hypertonie und Sklerose der Blutstrombahn; F. Lange, 1042
Lymphatics, Lymph and Lymphoid Tissue: Their Physiological and Clinical Significance; C. K. Drinker and J. M. Yoffey, 1040
Man's Greatest Victory Over Tuberculosis; J. A. Myers, 374
Manual of Physical Diagnosis; M. Lewison, E. B. Frelich and G. C. Coe, 372
March of Medicine, 849
Medical Aspects of Boxing; E. Jokl, 662
Microbes Which Help to Destroy Us; P. W. Allen, D. F. Holtman and L. A. McBee, 1042
Modern Treatment of Syphilis; J. E. Moore and others, 1246
Objective and Experimental Psychiatry; D. E. Cameron, 1040
Physical Medicine; F. H. Krusen, 848
Preeclamptic and Eclamptic Toxemia of Pregnancy; L. Dexter and S. Weiss, 1246
Radiologic Physics; C. Weyl, S. R. Warren Jr. and D. B. O'Neill, 847
Role of Liver in Surgery; F. F. Boyce, 180
Story of Clinical Pulmonary Tuberculosis; L. Brown, 372
Symposium on Blood and Blood-Forming Organs, 178
Synopsis of Applied Pathological Chemistry; J. E. Andes and A. G. Eaton, 1041
Synopsis of Diseases of Heart and Arteries; G. R. Herrmann, 847
Textbook of Ophthalmology; S. R. Gifford, 850
Textbook of Pediatrics; J. P. C. Griffith and A. G. Mitchell, 849
Tratado de quimica normal y patologica de la sangre; L. Corona, 179
Ueber die Häufigkeit von Krankheiten: Tuberkulose, Ulkuskrankheit und Krebs; F. Reichert, 849
Vitamins K; H. R. Butt and A. M. Snell, 662

Brain: See Nervous System; etc.
Diseases: See Encephalitis
Bright's Disease: See Nephritis
Brill, I. C.: Primary pulmonary vascular sclerosis, 560
Bronchiectasis, natural history of; clinical, roentgenologic and pathologic study, 395
Bronchiolitis: See Bronchitis
Bronchitis, bronchiolitis fibrosa obliterans; report of case, 663

Brown, E.: Efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
Brugsch, H. G.: Acropachyderma with pachyperiostitis; report of case, 687
Buchanan, O. H.: Serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
Butt, E. M.: Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57

**Cancer:** See under names of organs and regions, as Pancreas; etc.
Capillaries, 602. See also Blood, vessels
Capps, R. B.: Cause of so-called side ache that occurs in normal persons; personal observations, 94
Carbohydrates: See also Dextrose; Glycogen; etc.
glycogen and carbohydrate metabolism, 134
metabolism in Addison's disease, 991
metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
vitamin deficiency and metabolism of, 153
Cardiovascular Diseases: See Blood vessels; Heart
Cardiovascular System: See Arteries; Blood vessels; Heart; etc.
Carotene and vitamin A content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
Carotid Sinus syndrome, 647
Chagas' Disease: See Trypanosomiasis
Chemotherapy: See under names of diseases, as Endocarditis; Influenza; Meningitis; Pneumonia; etc.
Chickenpox, blood picture in, 294
Chill, clinical and physiologic characteristics of, 241
Cholelithiasis: See Gallbladder, calculi
Choriomeningitis: See Meningitis
Cobb, S.: Review of neuropsychiatry for 1941, 1232
Coccidioidosis, pulmonary cavitation associated with coccidioidal infection, 1179
Cohen, S. E.: Hepatic function in patients with amyloidosis, 309
Cold, effect on extremities, 606
Coma: See Diabetes Mellitus
Communicable Diseases: See also Meningitis; Syphilis; etc.
infectious diseases; review of significant publications in 1940-1941, 325
therapy with sulfanilamide and its derivatives, 325
Conn, E. S.: Metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
Metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
Metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
Conn, J. W.: Metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
Metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
Metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
Consolazio, W. V.: Hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
Cowpox, milker's nodules, 360
Cyanosis; acrocyanosis, 620
Cysts: See under names of organs and regions

**Dameshek, W.:** "Primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
Davis, L.: Pinealectomies on young mammals, 176
Deficiency Diseases: See also Diet and Dietetics; Nutrition; Vitamins; etc.
review of literature, 837
Dementia Praecox, hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
de Takáts, G.: Critical review of surgical treatment of vascular diseases, 636
Vascular diseases; seventh annual review, 599
Dextrose: See also Blood, sugar; Carbohydrates; etc.
tolerance test; importance in diagnosis of marginal malnutrition, 945
Diabetes Insipidus and antidiuretic principle of posterior lobe of pituitary gland, 170
and diabetes mellitus, 149
Diabetes Mellitus: See also Blood sugar
and acromegaly, 148
and diabetes insipidus, 149
and metabolism; review of certain recent contributions, 134
and ocular conditions and neuritis, 152
and pancreatic lesions, 149
and vascular disease, 151
associated with pregnancy, 142
diabetic coma, 151
diabetogenic action of extracts of anterior lobe of pituitary gland, 166
diagnosis, 141
diet in, 154
efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
incidence and mortality, 138
juvenile, 147
miscellaneous acute complications and diabetic coma, 149
pancreas and organs of secretion, 147
traumatic factors, 141
vitamin deficiency and metabolism of carbohydrate, 153
Diatheses, hemorrhagic; analysis of 355 autopsy reports, 112
Diet and Dietetics: See also Nutrition; Vitamins; etc.
metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
Digestive Tract: See Gastrointestinal Tract; Intestines; Stomach; etc.
Diuresis and Diuretics: See also Diabetes Insipidus; Kidneys
diabetes insipidus and antidiuretic principle of posterior lobe of pituitary gland, 170
Donath-Landsteiner Phenomenon: See Hemoglobinuria
Dozzi, D. L.: Origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
Drugs, effect on extremities, 608
Duodenum, Ulcers: See Peptic Ulcer
Dysentery, bacillary, 350

**Eagle, H.:** Biologic false positive serologic reactions in tests for syphilis; occurrence in normal persons, 898
Biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
Ebert, R. V.: Response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
Ecthyma contagiosum, 360
Edema: See Kidneys
Electrocardiogram: See under Heart
Electrolytes, metabolism in Addison's disease, 981
Embolism: See also Thrombosis
and thrombosis, 612
arterial occlusions, 641
therapy, 623

Embolism—Continued
thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
venous occlusions, 638
Encephalitis, equine, 359
Endocarditis, chemotherapy of subacute bacterial endocarditis, 331
Endocrine Glands, pancreas and organs of secretion in diabetes mellitus, 147
Energy Exchange: See Metabolism
Enzer, N.: State of motor centers in circulatory insufficiency, 498
Enzymes, bactericidal, 366
Epinephrine: See Adrenal Preparations
Epstein, E. Z.: Rheumatic pneumonia, 1074
Erythrocytes: See also Anemia; etc.
elliptic, in man, 1043
production; transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
Erythropoiesis: See Erythrocytes, production
Esophagus, diseases; review of literature, 788
Exercise, cause of so-called side ache that occurs in normal persons; personal observations, 94
tests, 622
Extremities, acropachyderma with pachyperiostitis; report of case, 687
blood flow, 599
Blood Supply: See also Blood vessels; Embolism; Raynaud's Disease; Thromboangiitis obliterans; etc.
blood supply; critical review of surgical treatment of vascular diseases, 636
blood supply; sympathectomy in treatment of peripheral circulatory disturbances, 649
blood supply; vascular diseases; seventh annual review, 599
effect of cold on, 606
effect of drugs on, 608
Paralysis: See Poliomyelitis
vascular disease and diabetes, 151
Eyes, diabetes and ocular conditions and neuritis, 152

**Fat**, origin of ketone bodies from fats and their regulation, 674
Fatigue, state of motor centers in circulatory insufficiency, 498
Favre-Nicolas' Disease: See Lymphogranuloma Venereum
Feces, determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
Fever: See Typhoid; etc.
Fluids, changes in body fluids in Addison's disease, 985
Fox, T. A.: Hemorrhagic diatheses; analysis of 355 autopsy reports, 112
Freyberg, R. H.: Serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
Friedländer Bacillus: See Bacteria, mucosus capsulatus group
Fusospirochetosis; recovery of causative organisms from blood with report of 2 cases, 80

**Gallbladder**, calculi; chemical factors in formation of gallstones, 1037
Gallstones: See Gallbladder, calculi
Gastric Ulcer: See Peptic Ulcer
Gastroenterology, clinical aspects, 788
physiologic aspects, 763
review of literature from July 1940 to July 1941, 763
Gastrointestinal Tract: See also Intestines; Stomach; etc.
infectious and parasitic diseases, 826
Gibson, J. G., II.: Response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
Gilbert, G. G.: Clinical lipoid nephrosis with reference to its transformation into clinical and pathologic chronic glomerulonephritis, 591
Gilligan, D. R.: Acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
Glomerulonephritis: See under Nephritis
Glycogen and carbohydrate metabolism, 134
Gonococci, infections, 366
infections, chemotherapy of, 333
Gottlieb, J.: Treatment of pneumococcic meningitis with sulfanilamide and sulfapyridine; statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum, 211
Goudsmit, A., Jr.: Acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
Greenspan, E. B.: Rheumatic pneumonia, 1074

**Haemophilus** Influenzae: See Influenza
Hammack, R. W.: Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
Hart, J. F.: Blood sugar in case of complete hypophysectomy, 893
Heart: See also Blood, circulation; Endocarditis; etc.
adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
Diseases: See also Endocarditis; Myocarditis; etc.
diseases; state of motor centers in circulatory insufficiency, 498
prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
Hematology: See Blood
Hemoglobin and Hemoglobin Compounds: See Anemia; Blood; Erythrocytes; Hemoglobinuria
Hemoglobinuria, acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
Hemorrhage, response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578
Hepatitis: See under Liver
Hildebrand, A. G.: Metabolism and diabetes; review of certain recent contributions, 134
Holbrook, A. A.: Blood picture in chickenpox, 294
Hormones: See Adrenal Preparations; Insulin; etc.
Hunter, W. C.: Thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
Hydrophobia: See Rabies
Hyperinsulinism: See under Insulin
Hypertension: See Blood pressure, high
Hypertrophy: See under names of organs and regions
Hypoglycemia: See Blood sugar
Hypophysis: See Pituitary Body
Hypopituitarism: See Pituitary Body
Hypotension: See Blood pressure, low
Hypothermia: See Temperature

**Icterus**: See Jaundice
Industrial Diseases, American Conference on Industrial Health, 846
Infantile Paralysis: See Poliomyelitis
Infarction: See under Heart
Infection: See also Bacteremia; and under names of bacteria, as Gonococci; Streptococci; etc.
biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161

Infectious Diseases: See Communicable Diseases
Influenza, chemotherapy of, 335
Insulin: See also Diabetes Mellitus; Pancreas
hyperinsulinism, 163
metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
metabolism in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
metabolism in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
review of literature, 155
shock therapy, 160
types of, 156
Internal Secretions: See Endocrine Glands
Intestines: See Gastrointestinal Tract
small and large intestine; review of literature, 812
Iron, "primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
Islands of Langerhans: See Pancreas

**Jaundice**, acute, massive hemoglobinuria of obscure cause, with jaundice and anemia; report of case with clinical and hematologic studies and measurements of blood pigment metabolism, 957
differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
serum lipids in patients with rheumatoid arthritis and in patients with obstructive jaundice; comparative study, 18
Jesser, J. H.: Critical review of surgical treatment of vascular diseases, 636
Vascular diseases; seventh annual review, 599
Jones, C. M.: Gastroenterology; review of literature from July 1940 to July 1941, 763
Jones, O. P.: Transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042

**Kala-Azar**: See Leishmaniasis
Kean, B. H.: Blood pressure studies on West Indians and Panamanians living on Isthmus of Panama, 466
Keating, F. R.: Diseases of adrenal glands; tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances, 1010
Keefer, C. S.: Significance of bacteremia caused by Staphylococcus aureus; study of 122 cases and review of literature concerned with experimental infection in animals, 851
Keith, N. M.: Acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
Kepler, E. J.: Diseases of adrenal glands; Addison's disease, 979
Diseases of adrenal glands: tumors of adrenal cortex, diseases of adrenal medulla and allied disturbances, 1010
Ketone Bodies: See Blood, ketone bodies
Kidneys, abnormal function in Addison's disease, 984
adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
Diseases: See also Nephritis
diseases; clinical lipoid nephrosis with reference to its transformation into clinical and pathologic chronic glomerulonephritis, 591
edema; acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Kidneys—Continued
edema; acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
studies on "essential" hypertension; association of hypertension with organic renal disease, 261
Kirshbaum, J. D.: Tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
Krygier, J. J.: Primary pulmonary vascular sclerosis, 560

**LaDue**, J. S.: Bronchiolitis fibrosa obliterans; report of case, 663
Landsteiner-Donath Phenomenon: See Hemoglobinuria
Langerhans' Islands: See under Pancreas
Langmuir, A. D.: Immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
Lectures, Salmon Memorial Lectures, 1038
Legs: See also Extremities
shelter legs, 622
thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
Leishmaniasis, 361
Leptospirosis, 360
Leukocytes, blood picture in chickenpox, 294
Levine, R.: Origin of ketone bodies from fats and their regulation, 674
Levine, S. A.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
Levy, H. A.: Tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
Lipase in Blood: See under Blood
Lipids: See Blood, fats and lipoids
Lipoid Nephrosis: See Kidneys, diseases
Lithiasis: See Gallbladder, calculi
Liver, differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
Glycogen: See under Glycogen
hepatic function in patients with amyloidosis, 309
origin of ketone bodies from fats and their regulation, 674
vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
Lord, J. W., Jr.: Differentiation of intrahepatic and extrahepatic jaundice; response of plasma prothrombin to intramuscular injection of menadione (2-methyl-1, 4-naphthoquinone) as diagnostic aid, 199
Loughlin, E. H.: Treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
Lungs: See also Respiratory Tract; etc.
chemotherapy of acute pulmonary infections, 339
pulmonary cavitation associated with coccidioidal infection, 1179
torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
Lymphocytes, blood picture in chickenpox, 294
in Meningitis: See Meningitis
Lymphogranuloma Venereum, 365

**Magiday**, M.: Blood sugar in case of complete hypophysectomy, 893
Malnutrition: See Nutrition
Menadione: See Jaundice

Meningitis, chemotherapy of, 330
lymphocytic choriomeningitis, 356
pneumococcic; treatment with sulfanilamide and sulfapyridine; statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum, 211
Meningococci: See under Meningitis
Mental Diseases: See also Dementia Praecox; Neuroses and Psychoneuroses; etc.
electric shock therapy for psychoses, 1236
insulin shock therapy, 160
neurologic approach to mental disorder, 1244
Metabolism and diabetes; review of certain recent contributions, 134
hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
in organic hyperinsulinism; effects of epinephrine on glycemic level and on combustion of carbohydrate, 1105
in organic hyperinsulinism; quantitative studies of variations in rate of combustion of carbohydrate produced by alterations in diet, 876
Milker's Nodules: See Cowpox
Miller, E. B.: "Primary" hypochromic anemia terminating in pernicious anemia; report of 2 cases, 375
Mohr, C. F.: Biologic false positive serologic reactions in tests for syphilis; occurrence in normal persons, 898
Biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
Moore, J. E.: Biologic false positive serologic reactions in tests for syphilis; occurrence in normal persons, 898
Biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161
Muscles, cervical rib and scalenus syndrome, 648

**Nephritis:** See also Kidneys, diseases
acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
clinical lipoid nephrosis with reference to its transformation into clinical and pathologic chronic glomerulonephritis, 591
origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
Nephrosis: See Kidneys, diseases; Nephritis
Nerves: See Neuritis
Nervous System, state of motor centers in circulatory insufficiency, 498
torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
Neuritis, diabetes and ocular conditions and neuritis, 152
Neuropsychiatry, neurologic approach to mental disorder, 1244
review for 1941, 1232
Neuroses and Psychoneuroses: See also Mental Diseases; etc.
war neuroses, 1232
Neutrophils: See Leukocytes
Nicolas-Favre's Disease: See Lymphogranuloma Venereum
Nissl Bodies: See Rabies
Nitrogen, metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
Nutrition: See also Diet and Dietetics; Vitamins; etc.
importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945

**Obesity,** 172
Ogilvie, A. G.: Natural history of bronchiectasis; clinical, roentgenologic and pathologic study, 395
Old Age, thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
Oscillometry: See under Arteries
Osmosis and Permeability, acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Owens, L. B.: Efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066

**Pachyperiostitis:** See Periostitis
Pain, cause of so-called side ache that occurs in normal persons; personal observations, 94
Paley, K.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
Panamanians: See Races
Pancreas and organs of secretion in diabetes mellitus, 147
diagnosis of carcinoma of, 525
pancreatic lesions and diabetes, 149
Papper, E.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
Paralysis, Infantile: See Poliomyelitis
Patch Tests: See Anaphylaxis and Allergy
Pearlman, A. W.: Hepatic function in patients with amyloidosis, 309
Pecora, L. J.: Hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
Peptic Ulcer, review of literature, 801
treatment with posterior pituitary preparation, 172
Perera, G. A.: Clinical and physiologic characteristics of chill, 241
Periarteritis nodosa, 616
Periostitis, acropachyderma with pachyperiostitis; report of case, 687
Perlman, L.: Hemorrhagic diatheses; analysis of 355 autopsy reports, 112
Pineal Gland, pinealectomies on young mammals, 176
Pituitary Body, blood sugar in case of complete hypophysectomy, 893
hypopituitarism and Simmonds' disease, 172
review of literature, 165
tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
Pituitary Preparations, diabetes insipidus and antidiuretic principle of posterior lobe of pituitary gland, 170
diabetogenic action of extracts of anterior lobe of pituitary gland, 166
treatment of peptic ulcer with posterior pituitary preparation, 172
Placenta, transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
Plague, 353
Pneumococci: See also Pneumonia
immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
Meningitis: See Meningitis
Pneumonia, chemotherapy of pneumococcic lobar pneumonia, 328
Friedländer, 348
hemolytic streptococcic, 347
immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25

Pneumonia—Continued
pneumococcic, 344
review of literature, 343
rheumatic, 1074
staphylococcic, 348
treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
Poisons and Poisoning: See under names of substances
Poliomyelitis, 356
Polyuria: See Diabetes Insipidus
Power, M. H.: Acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Pregnancy, associated with diabetes mellitus, 142
Proteins, acacia in treatment of nephrotic syndrome; influence of acacia, injected intravenously, on concentration of proteins and on colloid osmotic pressure of serum, 701
Prothrombin: See Blood, coagulation
Psittacosis, 362
Psychoneurosis: See Neuroses and Psychoneuroses

**Raab**, W.: Adrenocortical compounds in blood; relation of their quantity to arterial hypertension, renal insufficiency and congestive heart failure, 713
Rabies, 361
Races, blood pressure studies on West Indians and Panamanians living on Isthmus of Panama, 466
Ralli, E. P.: Vitamin A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
Ransmeier, J. C.: Direct cultivation of Bacterium tularense from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
Raynaud's Disease, 618
Reed, E. A.: Immediate serum reaction in man; classification and analysis of reaction to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
Reeves, D. L.: Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
Reflex, Carotid Sinus: See Carotid Sinus
Reimann, H. A.: Infectious diseases; review of significant publications in 1940-1941, 325
Respiratory Tract, chemotherapy of acute infections of, 335
vaccines for infections of, 343
Reticuloendothelial System: See Anemia; Jaundice; etc.
Retinitis pigmentosa, 621
Rheumatic Fever, 349
rheumatic pneumonia, 1074
Ribs, abnormalities; cervical rib and scalenus syndrome, 648
Rickettsia; rickettsial diseases, 364
Robertson, T. D.: Thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
Robinson, G. W., Jr.: Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
Rogers, E. S.: Immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
Rosenbaum, F. F.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
Rutstein, D. D.: Immediate serum reactions in man; classification and analysis of reactions to intravenous administration of antipneumococcus horse serum in cases of pneumonia, 25
Rynearson, E. H.: Metabolism and diabetes; review of certain recent contributions, 134

**Salmon** Memorial Lectures, 1039
Scalenotomy: See Muscles
Schaub, I. G.: Direct cultivation of Bacterium tularense from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
Schistosomiasis, 361
Schizophrenia: See Dementia Praecox
Schlesinger, M. J.: Multiple fresh coronary occlusions in patients with antecedent shock, 181
Schroeder, H. A.: Studies on "essential" hypertension; association of hypertension with organic renal disease, 261
Scleroderma; acrosclerosis, 620
Scupham, G. W.: Vascular diseases; seventh annual review, 599
Secretions, Internal: See Endocrine Glands
Senility: See Old Age
Sensitization: See Anaphylaxis and Allergy
Serum: See Blood
Shelton, P.: Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
Shigella Dysenteriae: See Dysentery
Shock, multiple fresh coronary occlusions in patients with antecedent shock, 181
Shoulder, cervical rib and scalenus syndrome, 648
Simmonds' Disease: See under Pituitary Body
Simonson, E.: State of motor centers in circulatory insufficiency, 498
Sinus, Carotid: See Carotid Sinus
Skin, acropachyderma with pachyperiostitis; report of case, 687
Skinner, D.: Significance of bacteremia caused by Staphylococcus aureus; study of 122 cases and review of literature concerned with experimental infection in animals, 851
Smith, F. V., Jr.: Importance of dextrose tolerance test in diagnosis of marginal malnutrition, 945
Sneeden, V. D.: Thrombosis of deep veins of legs; its clinical significance as exemplified in 351 autopsies, 1
Snyder, G. A. C.: Thrombosis of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
Societies, American Conference on Industrial Health, 846
Association of Military Surgeons of United States, 661
Mississippi Valley Medical Society, 369
Sodium, Bicarbonate: See Ketosis
metabolism in organic hyperinsulinism; effects of adrenal cortical extract on blood sugar and on sodium and nitrogen equilibrium, 1115
Soskin, S.: Origin of ketone bodies from fats and their regulation, 674
Spaeth, R.: Therapy of tetanus; study of 276 cases, 1133
Spherocytosis: See under Erythrocytes
Spitz, S. H.: Treatment of lobar pneumonia with rabbit antipneumococcus serum; efficacy of projected dose method of treating pneumonia with homologous refined and unconcentrated rabbit antipneumococcus serum, 121
Staphylococci, chemotherapy of staphylococcic infections, 333
significance of bacteremia caused by Staphylococcus aureus; study of 122 cases and review of literature concerned with experimental infection in animals, 851
Stead, E. A., Jr.: Response of normal subjects to acute blood loss with reference to mechanism of restoration of blood volume, 578

**Steele, C. W.:** Treatment of pneumococcic meningitis with sulfanilamide and sulfapyridine; statistical study of all reported cases in which chemotherapy was used, with or without specific antipneumococcus serum, 211
**Steele, J. M.:** Studies on "essential" hypertension; association of hypertension with organic renal disease, 261
Sterilization of air, 367
Stomach: See also Gastrointestinal Tract
transmission of antianemic principle across placenta and its influence on embryonic erythropoiesis; quantitative effect of diets containing ventriculin, 476; correction, 1042
Ulcers: See Peptic Ulcer
Stools: See Feces
Streptococci, chemotherapy of hemolytic streptococcic infection, 332
rheumatic fever, 349
Sugar in Blood: See Blood, sugar
Sulfanilamide and Sulfanilamide Derivatives, Therapy: See under Communicable Diseases; Meningitis; Pneumonia; etc.
Sulfapyridine, Therapy: See Meningitis
Suprarenal Preparations: See Adrenal Preparations
Suprarenals: See Adrenals
Surgery, military; Association of Military Surgeons of United States, 661
Sympathectomy: See Extremities, blood supply
Syphilis: See also under names of organs and regions
biologic false positive serologic reaction in in tests for syphilis; occurrence in normal persons, 898
biologic false positive serologic reactions in tests for syphilis; occurrence with organic diseases other than syphilis, 1161

**Talbott, J. H.:** Hypothermia; report of case in which patient died during therapeutic reduction of body temperature with metabolic and pathologic studies, 1120
Temperature: See also Cold
cutaneous, 610
hypothermia; report of case in which patient died during therapeutic reduction of body temperature, with metabolic and pathologic studies, 1120
Tetanus, 352
therapy; study of 276 cases, 1133
Thromboangiitis obliterans, 614
Thrombosis: See also Embolism
and embolism, 612
arterial occlusions, 641
multiple fresh coronary occlusions in patients with antecedent shock, 181
of deep veins of leg; its clinical significance as exemplified in 351 autopsies, 1
prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; immediate prognosis, 913
prognostic value of various clinical and electrocardiographic features of acute myocardial infarction; ultimate prognosis, 1215
therapy, 623
venous occlusions, 638
Tiber, A. M.: Hepatic function in patients with amyloidosis, 309
Tick Fevers; Colorado tick fever, 364
Torula infection of lungs and central nervous system; report of 6 cases with 3 autopsies, 57
Toxoplasmosis, 362
Trauma, traumatic factor in diabetes mellitus, 141
Trypanosomiasis; Chagas' disease, 363
Tuberculoma of hypophysis with insufficiency of anterior lobe; clinical and pathologic study of 2 cases, 1095
Tuberculosis: See under names of organs and regions, as Pituitary Body; etc.
Tularemia, direct cultivation of Bacterium tularense from human blood drawn during life and at autopsy; report of 3 fatal cases of tularemia with brief notes on 2 others, 747
Tumors: See under names of organs and regions, as Adrenals; etc.
Typhoid, 351

**Ulcers, Peptic:** See Peptic Ulcer
Uranium Nephritis: See under Nephritis
Urine: See also Diuresis and Diuretics; etc.
acacia in treatment of nephrotic syndrome with reference to excretion of chloride and water; report of cases, 513
determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
origin of blood amylase and blood lipase in dog; relation between blood amylase and urinary amylase following induction of uranium nephritis, 232
Urobilinogen: See under Urine

**Van Deilen, T. R.:** Vascular diseases; seventh annual review, 599
Vasomotor System: See Arteries; Blood vessels; Capillaries; Veins
Veins: See also Blood vessels; Embolism; Thrombosis
exercise test, 622
Venous Pressure: See Blood pressure
Ventriculin: See under Stomach
Viruses, neurotropic, 355
Vitamins: See also Deficiency Diseases; Diet and Dietetics; etc.
A and carotene content of human liver in normal and in diseased subjects; analysis of 116 human livers, 102
deficiency and metabolism of carbohydrate, 153
K: See Blood, coagulation

**War:** See also Air Raids; Surgery, military; etc.
neuroses, 1232
**Watson, C. J.:** Determination of urobilinogen in feces and in urine; comparison of Sparkman and Watson procedure, 740
**Williams, R. H.:** Fusospirochetosis; recovery of causative organisms from blood with report of 2 cases, 80
**Willson, D. M.:** Diseases of adrenal glands; Addison's disease, 979
**Winn, W. A.:** Pulmonary cavitation associated with coccidioidal infection, 1179
**Winship, T. O.:** Elliptic erythrocytes in man, 1043
**Wright, J.:** Efficacy of intravenous sodium bicarbonate therapy in treatment of diabetic ketosis, 1066
**Wyandt, H.:** Elliptic erythrocytes in man, 1043

**Zoll, P. M.:** Multiple fresh coronary occlusions in patients with antecedent shock, 181

JAN 2 1942

Medical Library

VOLUME 68 NUMBER 6

# ARCHIVES

OF

# INTERNAL MEDICINE

EDITORIAL BOARD

N. C. GILBERT, Chief Editor, Chicago

ARTHUR BLOOMFIELD, San Francisco J. H. MUSSER, New Orleans

REGINALD FITZ, Boston RUSSELL M. WILDER, Rochester, Minn.

DECEMBER 1941

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

COPYRIGHT, 1941, BY THE AMERICAN MEDICAL ASSOCIATION

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and for the reporting of research and observation in the domain of internal medicine.

Manuscripts for publication, books for review and correspondence relating to the editorial management should be sent to the Chief Editor, Dr. N. C. Gilbert, 535 North Dearborn Street, Chicago. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE or in any of the other publications issued by the Association will not be permitted.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $5.00; Canadian, $5.40; foreign, $6.00, including postage. Single copies are 75 cents, postpaid.

Checks, money orders and drafts should be made payable to the American Medical Association.

## OTHER PERIODICAL PUBLICATIONS
### of the American Medical Association

**THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION**—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $9.50; foreign, $12.00. Single copies, 25 cents.

**AMERICAN JOURNAL OF DISEASES OF CHILDREN**—Monthly. Presents pediatrics as a medical science and as a social problem. Includes carefully prepared reviews, based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $5.00; Canadian, $5.40; foreign, $6.00. Single copies, 75 cents.

**ARCHIVES OF NEUROLOGY AND PSYCHIATRY**—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $5.00; Canadian, $5.40; foreign, $6.00. Single copies, 75 cents.

**ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY**—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and abstracts of the literature on these two subjects, transactions of the important dermatologic societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $5.00; Canadian, $5.40; foreign, $6.00. Single copies, 75 cents.

**ARCHIVES OF SURGERY**—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): domestic, $5.00; Canadian, $5.40; foreign, $6.00. Single copies, 75 cents, except special numbers.

**ARCHIVES OF OTOLARYNGOLOGY**—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $6.00; Canadian, $6.60; foreign, $7.00. Single copies, 75 cents.

**ARCHIVES OF PATHOLOGY**—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.60; foreign, $7.00. Single copies, 75 cents, except special issues.

**ARCHIVES OF OPHTHALMOLOGY**—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $5.00; Canadian, $5.40; foreign, $6.00. Single copies, 75 cents.

**WAR MEDICINE**—Bimonthly. Devoted to material on preparedness and scientific advancement in relation to military, naval, public health and allied services. Annual subscription price: domestic, $5.00; Canadian, $5.40; foreign, $6.00. Single copies, $1.25.

**QUARTERLY CUMULATIVE INDEX MEDICUS**—Quarterly. A complete subject and author index to the worth while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: domestic, $12.00; Canadian, $14.00; foreign, $14.00.

**AMERICAN MEDICAL ASSOCIATION**

535 North Dearborn Street — CHICAGO

# CONTENTS


PAGE

Elliptic Erythrocytes in Man. Helen Wyant, M.S., Omaha; Paul M. Bancroft, M.D., Lincoln, Neb., and Theodore O. Winship, M.D., Rizal, Philippine Islands ..... 1043

Efficacy of Intravenous Sodium Bicarbonate Therapy in the Treatment of Diabetic Ketosis. Louis B. Owens, M.D.; Jackson Wright, M.D., and Edna Brown, M.S., Cincinnati ..... 1066

Rheumatic Pneumonia. Emanuel Z. Epstein, M.D., and Edward B. Greenspan, M.D., New York ..... 1074

Tuberculoma of Hypophysis with Insufficiency of Anterior Lobe: A Clinical and Pathologic Study of Two Cases. Jack D. Kiserbaum, M.D., and Herman A. Levy, M.D., Chicago ..... 1095

Metabolism in Organic Hyperinsulinism. Jerome W. Conn, M.D., and Elizabeth Stern Conn, M.D., Ann Arbor, Mich.:

II. Effects of Epinephrine on Glycemic Level and on Combustion of Carbohydrate ..... 1105

III. Effects of Adrenal Cortical Extract on Blood Sugar and on Sodium and Nitrogen Equilibrium ..... 1115

Hypothermia: Report of a Case in Which the Patient Died During Therapeutic Reduction of Body Temperature, with Metabolic and Pathologic Studies. John H. Talbott, M.D.; W. V. Consolazio, B.S., and L. J. Pecora, B.S., Boston ..... 1120

Therapy of Tetanus: A Study of Two Hundred and Seventy-Six Cases. Ralph Spaeth, M.D., Chicago ..... 1133

Biologic False Positive Serologic Reactions in Tests for Syphilis: II. Occurrence with Organic Diseases Other than Syphilis. Charles F. Moore, M.D.; Joseph Earle Moore, M.D., and Harry Eagle, M.D., Baltimore ..... 1161

Pulmonary Cavitation Associated with Coccidioidal Infection. William A. Winn, M.D., Springville, Calif. ..... 1179

Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction: II. Ultimate Prognosis. Samuel A. Levine, M.D., Boston, and Francis F. Rosenbaum, M.D., Ann Arbor, Mich. ..... 1215

Progress in Internal Medicine:

Review of Neuropsychiatry for 1941. Stanley Cobb, M.D., Boston 1232

Book Reviews ..... 1246

General Index ..... 1247